# The Vinylogous Aldol Reaction

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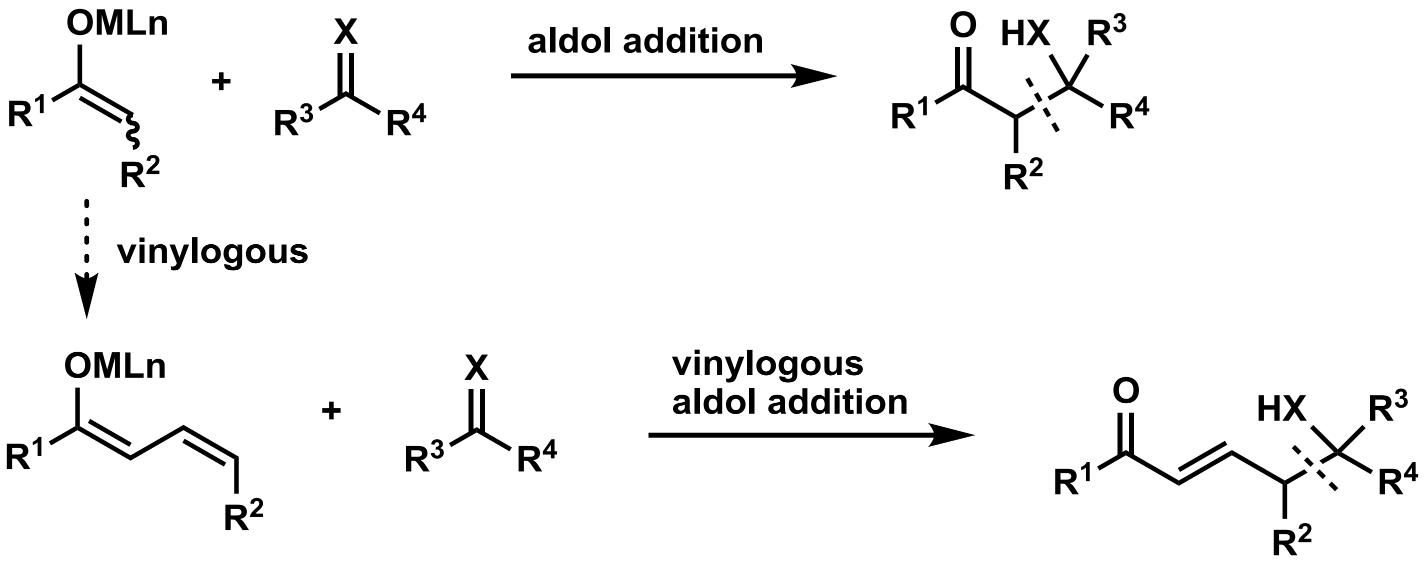
Zanardi, F. *et al*. *Chem. Rev*. **2000**, *100*, 1929
Zanardi, F. *et al.*. *Chem. Rev*. **2011**, *111*, 3076

# Introduction

*When, in a compound of the type $A{-}E_1{=}E_2$ or $A{-}E_1{\equiv}E_2$, a structural unit of the type $-(RC{=}CR)_n-$ is interposed between A and $E_1$ the function of $E_2$ remains qualitatively unchanged but that of $E_1$ may be usurped by the carbon atom attached to A.*[1]

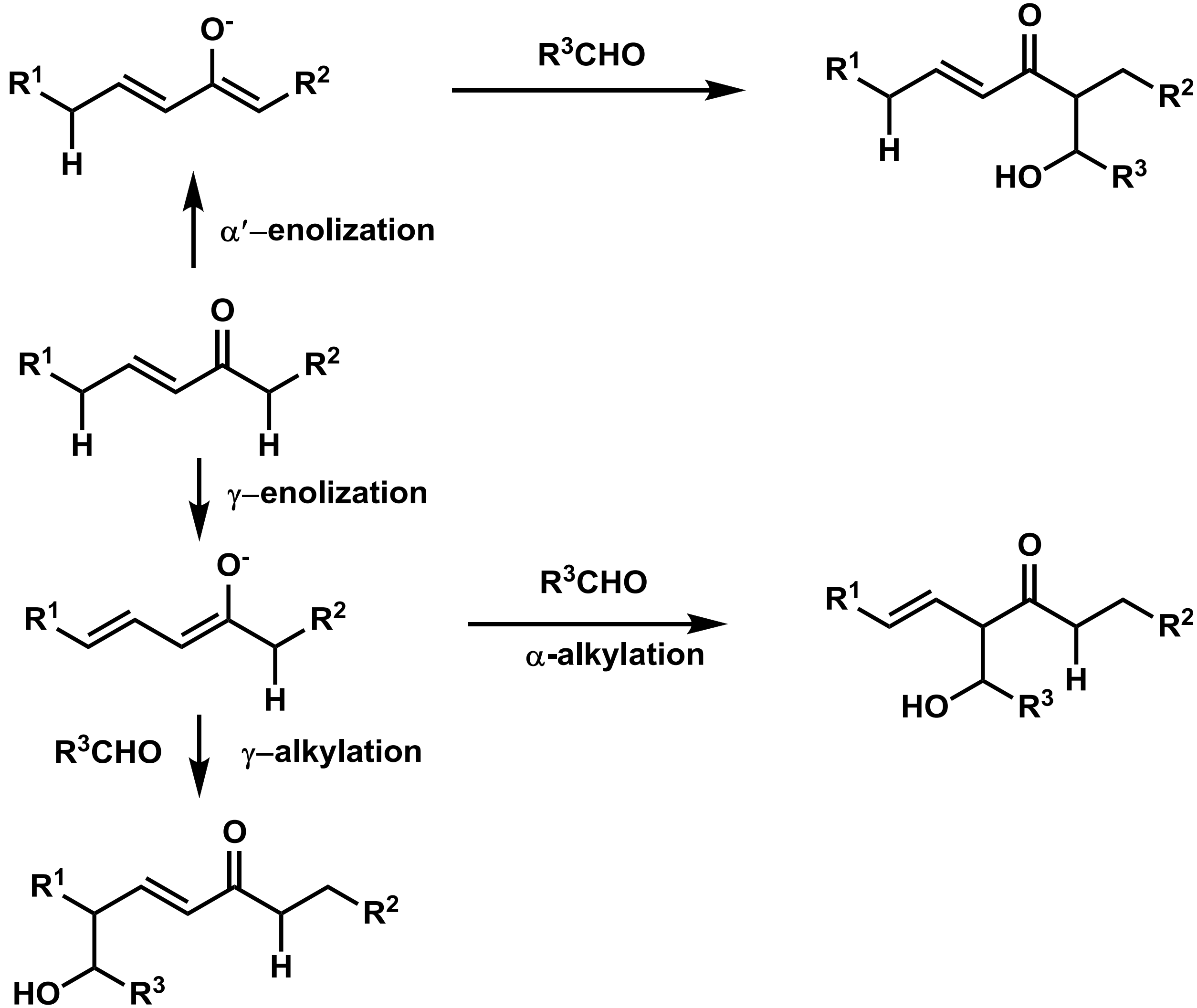
Reynold C. Fuson



# Regiochemical Issues

kinetic

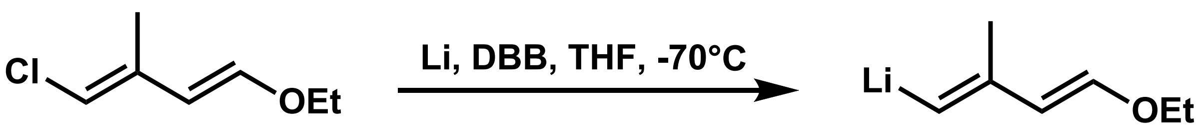
thermodynamic



# Dienolates

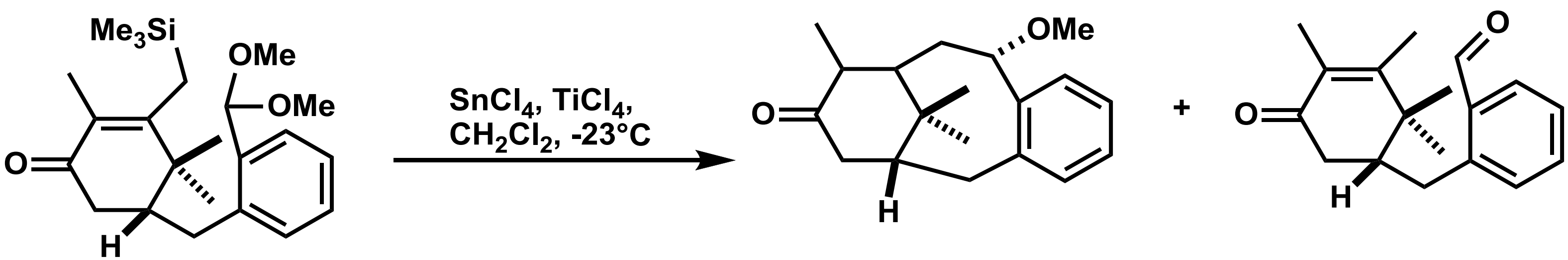
- From Unsaturated Aldehydes and Ketons
- 1. Prenal metal dienolates


(1)




(2)

- 2. γ-silyl strategy

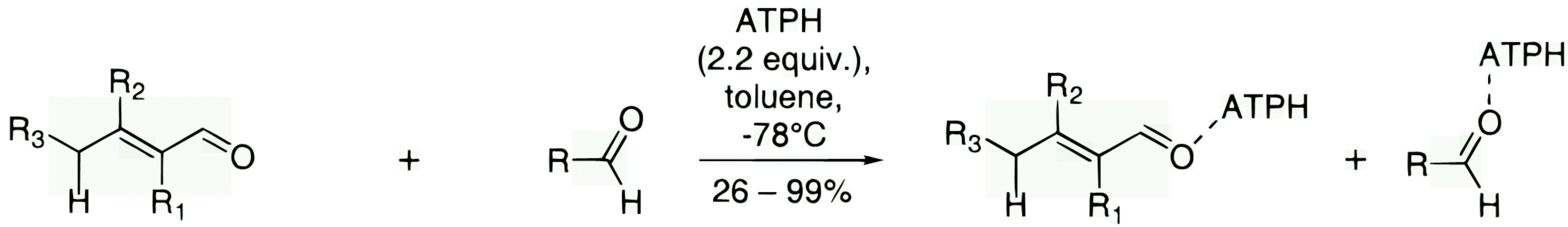



(3)


(1) Duhamel, L. *et al.* *Tetrahedron Lett*. **1998**, *39,* 7093
(2) Duhamel, P. *et al. Tetrahedron Lett*, **1998**, *39,* 8975
(3) Kuwajima, I. *et al.* *J. Am. Chem. Soc*. **1989,** *111*, 8277

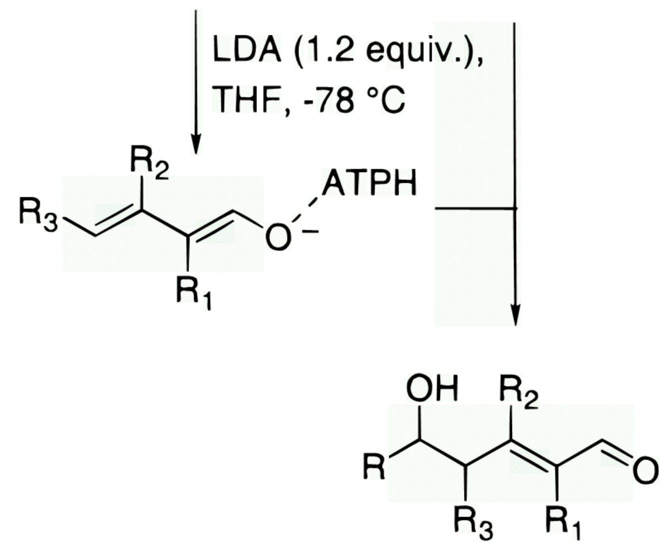
# Dienolates

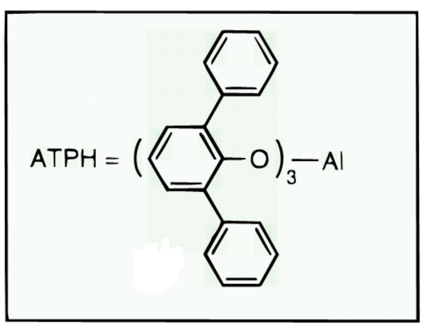
- From Unsaturated Aldehydes and Ketones
- 3. ATPH strategy




**a:** $R_1 = R_2 = R_3 = H$
**b:** $R_1$ = Me; $R_2 = R_3 = H$
**c:** $R_1 = R_3$ = H; $R_2$ = Me
**d:** $R_1 = R_2$ = H; $R_3$ = *E*-Me-CH=CH-
**e:** $R_1 = R_2$ =H; $R_3$ = *E,E*-Me-$(CH{=}CH)_2$-

**a:** Ph
**b:** $Bu^t$
**c:** $Bu^n$
**d:** Ph-CH=CH-

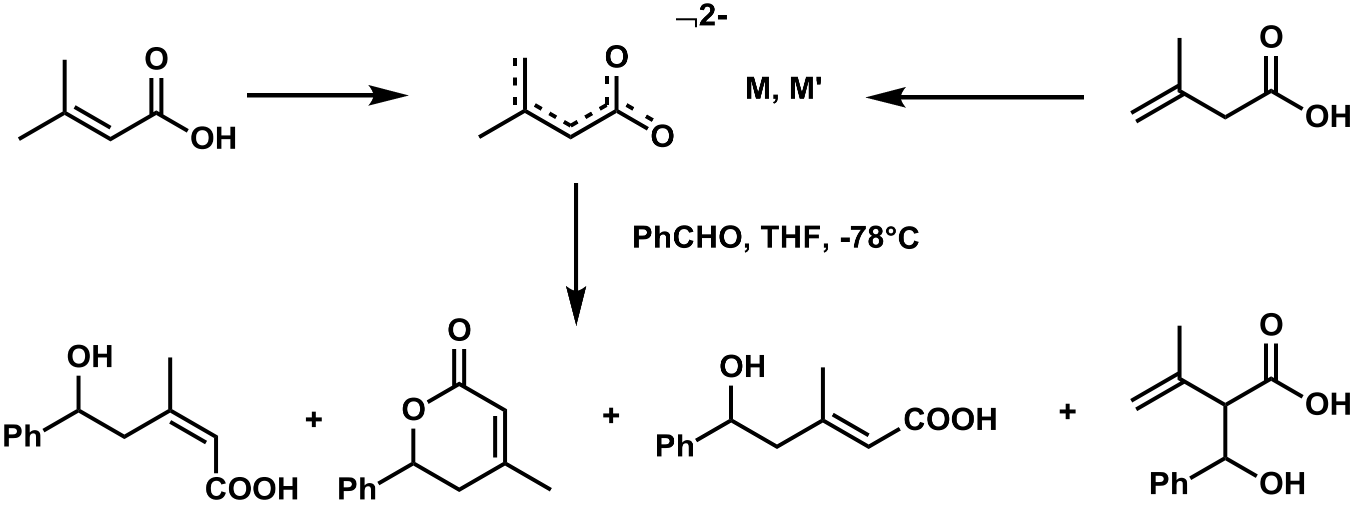



Yamamoto, H. *et al. J. Am. Chem. Soc*. **1998,** *120,* 813

# Dienolates

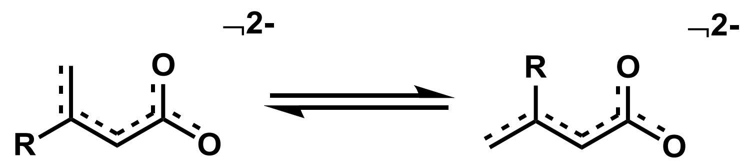
- From Unsaturated Carboxylic Acids




a b c d

| M | M' | a | b | c | d |
|---|---|---|---|---|---|
| Li | $SnBu_3$ | - | - | - | 100 |
| Li | Li | 19 | 27 | - | 54 |
| Na | Li | 5 | 44 | 5 | 46 |
| K | Li | 54 | 24 | - | 22 |
| K | K | 100 | - | - | - |

(relative yield (%) for a, b, c, d)



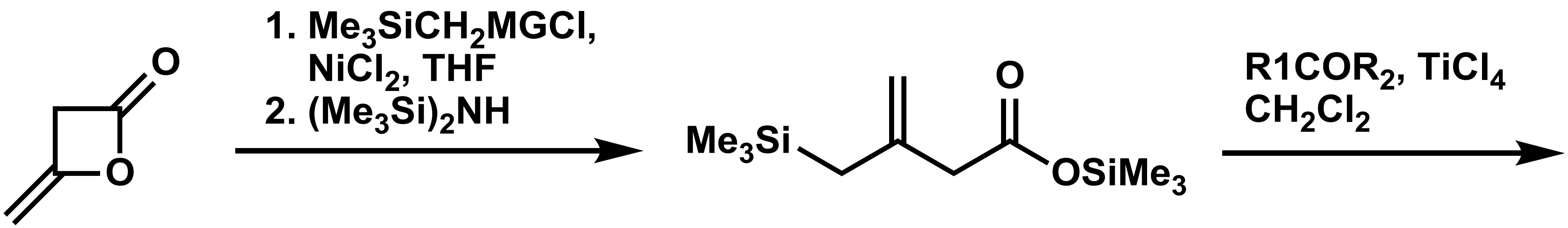

1e: R=Me
1f: R=H

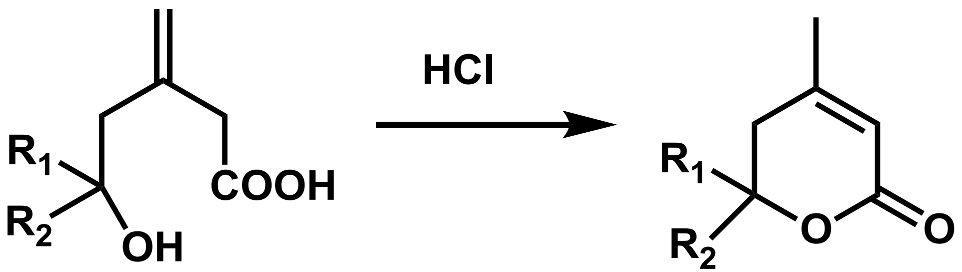
2e: R=Me
2f: R=H

Ronchi, A. *et al. J. Am. Chem. Soc. Perkin Trans*. **1973,** *1*, 400

# Dienolates

- From Unsaturated Carboxylic Acids



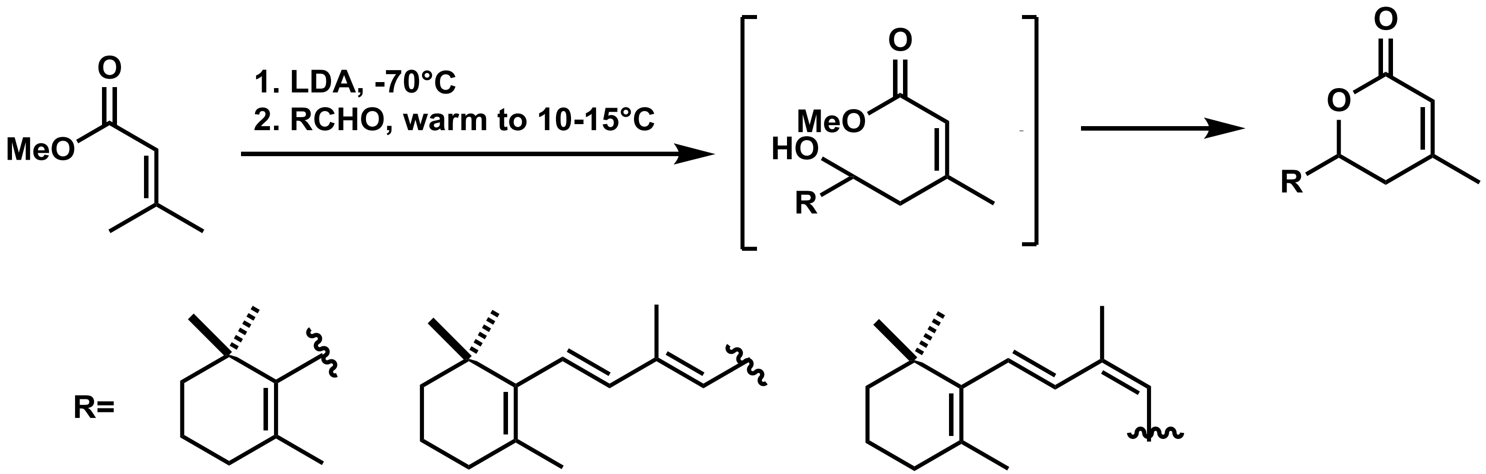




| $R_1$ | $R_2$ | yield (%) |
|---|---|---|
| H | $Pr^n$ | 81 |
| H | $Pr^i$ | 79 |
| H | $Bu^t$ | 78 |
| Me | Me | 80 |
| $-(CH_2-CH_2)_2-$ | | 78 |

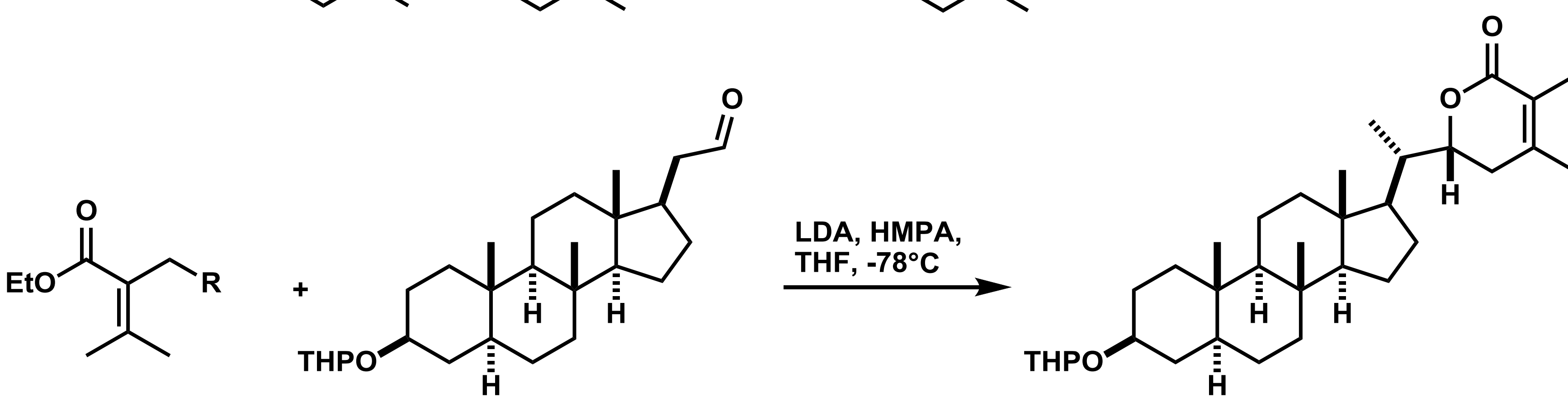
Kurachi, Y. *et al. J. Chem. Soc. Chem. Commum*. **1977**, 500

# Dienolates

- From Unsaturated Esters




(1)



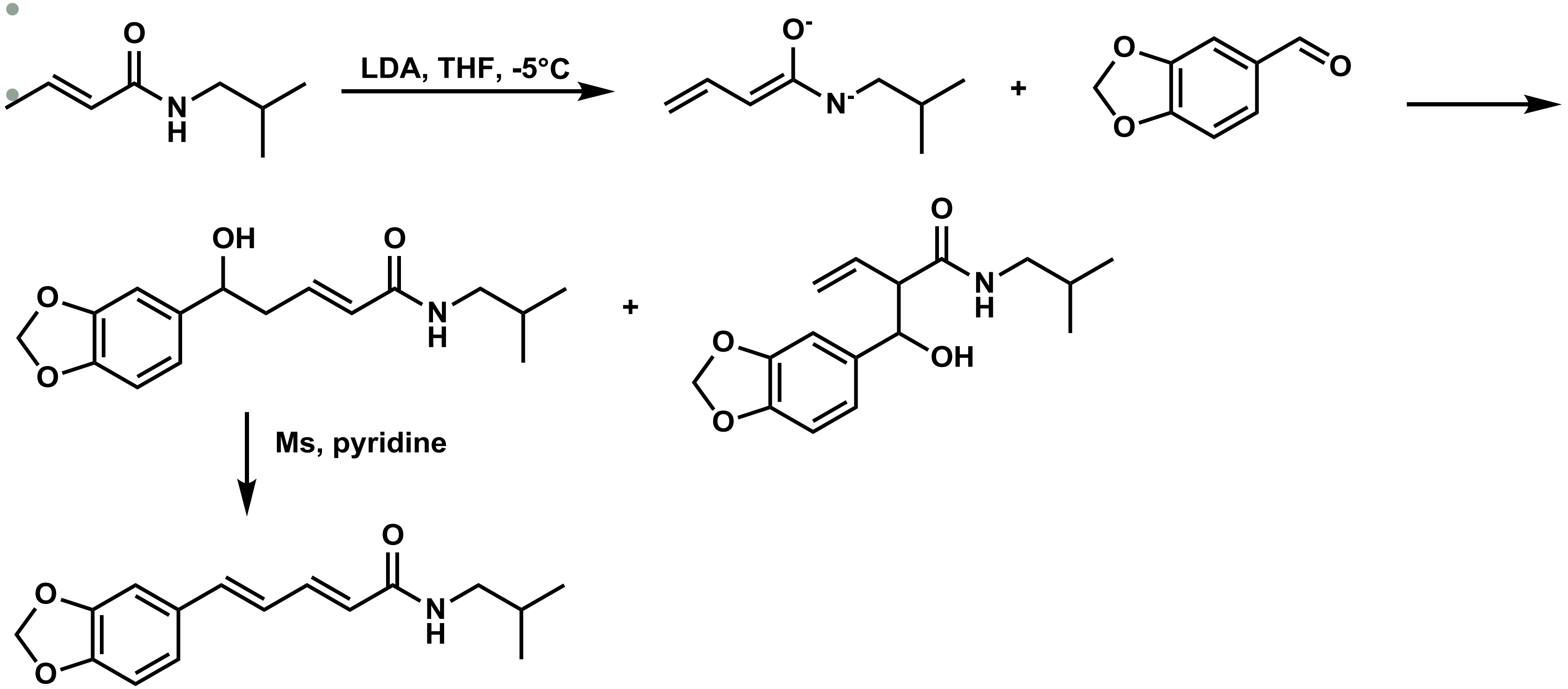

(2)

R=H, OH

(1) Heathcock, C. H. *et al. J. Org. Chem*, **1980**, *45,* 1181
(2) Ikekawa, N. *et al. Tetrahedron Lett.* **1975,** 4135

# Dienolates

- From Unsaturated Amides and Imides
-

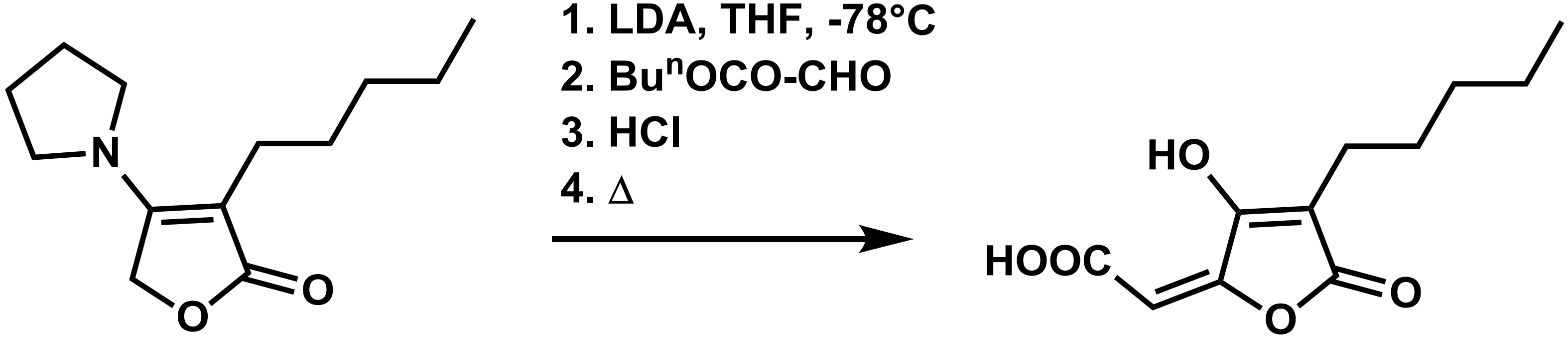



- chiral auxiliaries

Snieckus, V. *et al. J. Org. Chem*. **1981**, *46*, 2029

# Dienolates

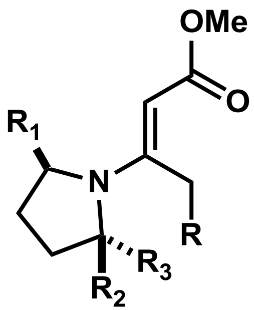
- From β-Heterosubstituted α,β-Unsaturated Carbonyls and Butenolides



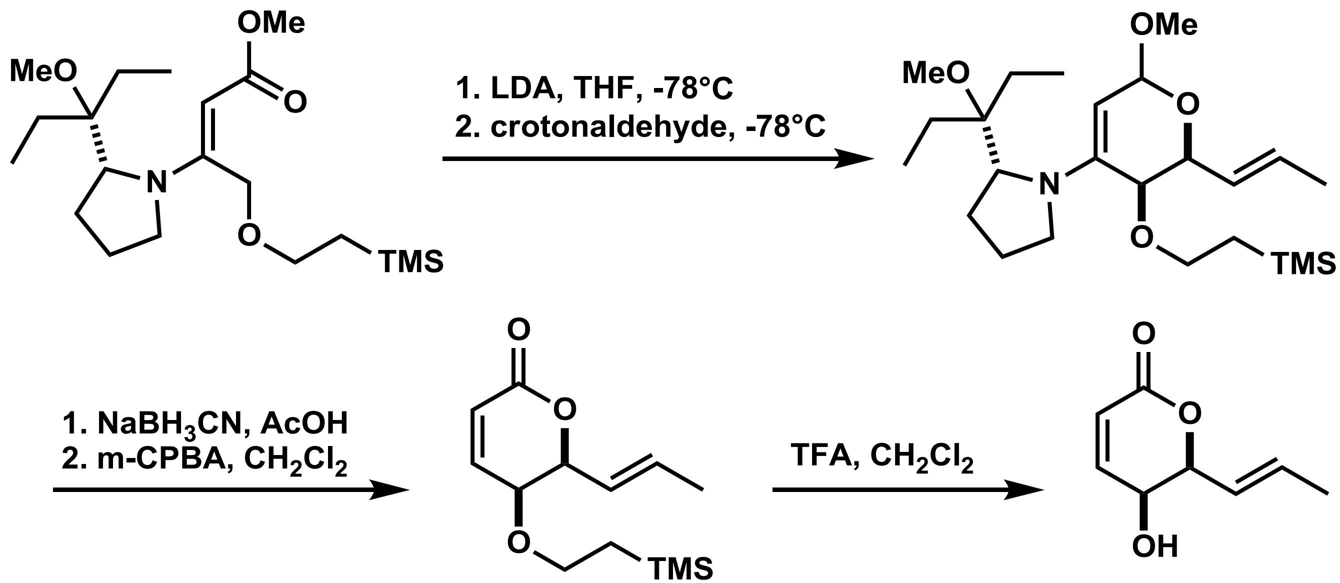

Holker, J. S. E. *et al. J. Chem. Soc. Chem. Commun*. **1979,** 81

# Dienolates

- From β-Heterosubstituted α,β-Unsaturated Carbonyls and Butenolides



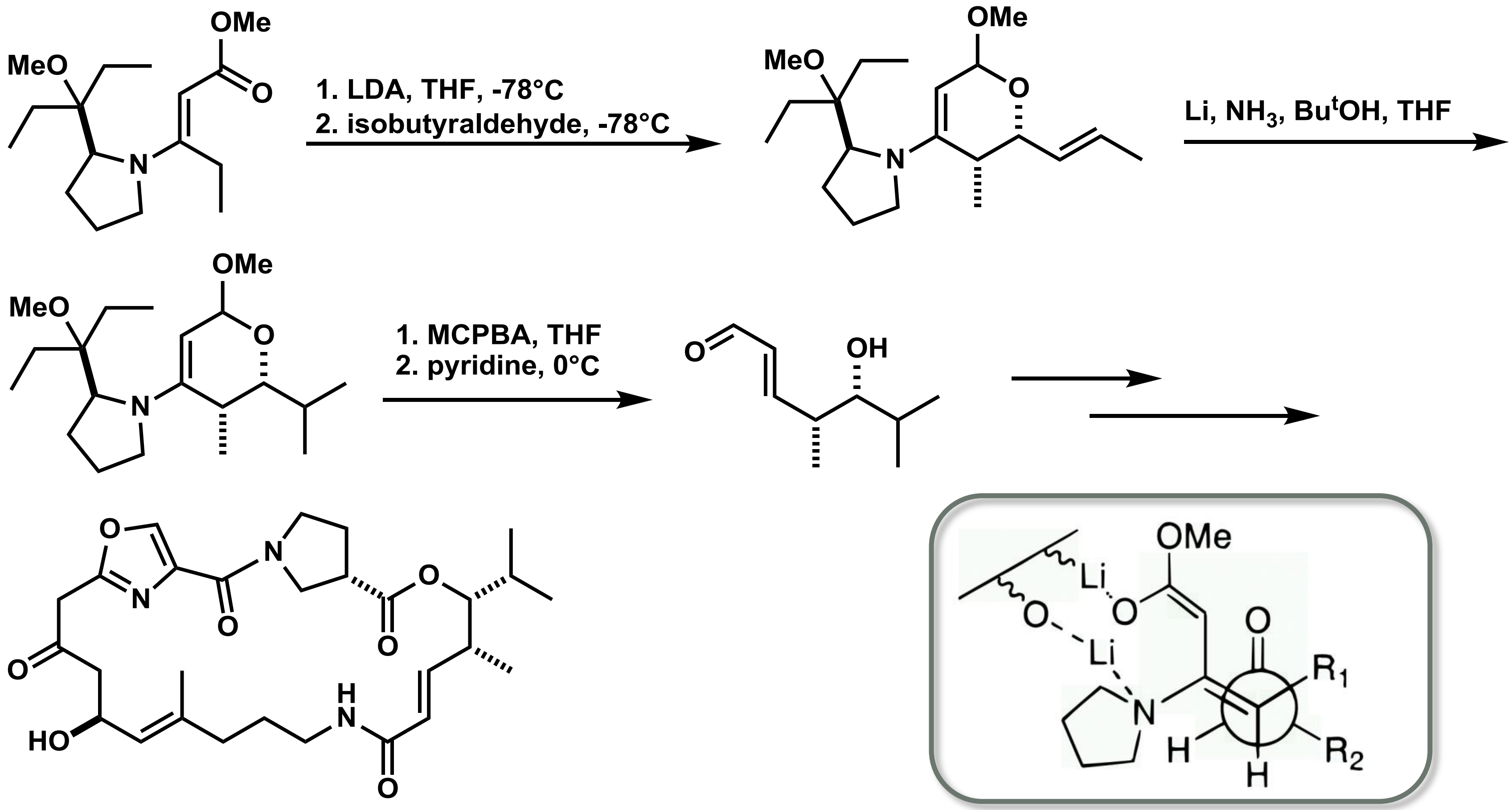

a: $R_1$=$R_3$=Me; $R_2$=H
b: $R_1$=$Et_2C(OMe)$-; $R_2$=$R_3$=H
*ent*-b: $R_1$=$R_3$=H; $R_2$=$Et_2C(OMe)$-




Gillman, K. W. *et al. Tetrahedron Lett*. **1999,** *40*, 1257

# Dienolates

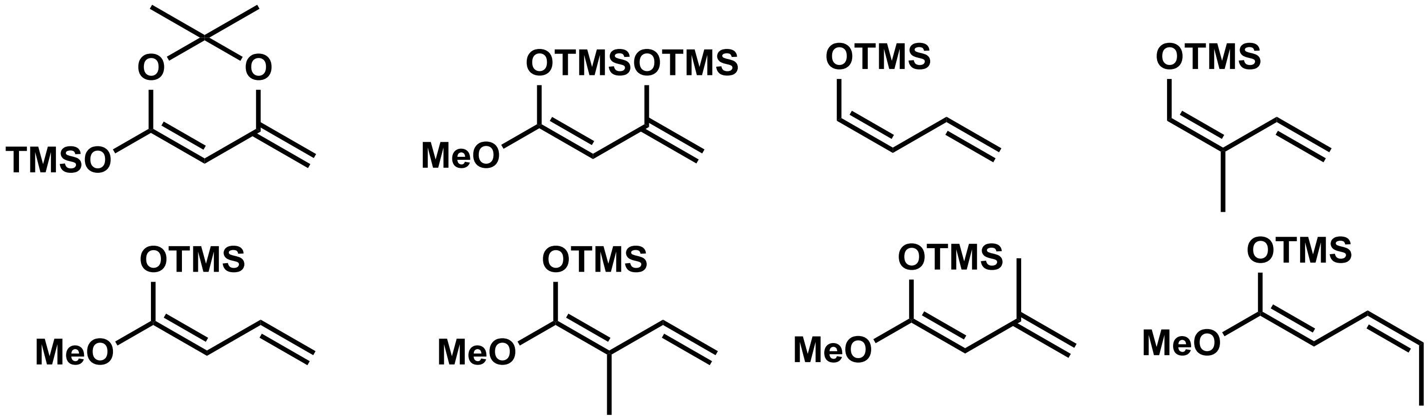
- From β-Heterosubstituted α,β-Unsaturated Carbonyls and Butenolides




Schlessinger, R. H. *et al. J. Am. Chem. Soc*. **1996,** *118*, 3301
Schlessinger, R. H. *et al. J. Org. Chem*. **1996**, *61*, 3226

# Diastereoselective and Unselective Processes
## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

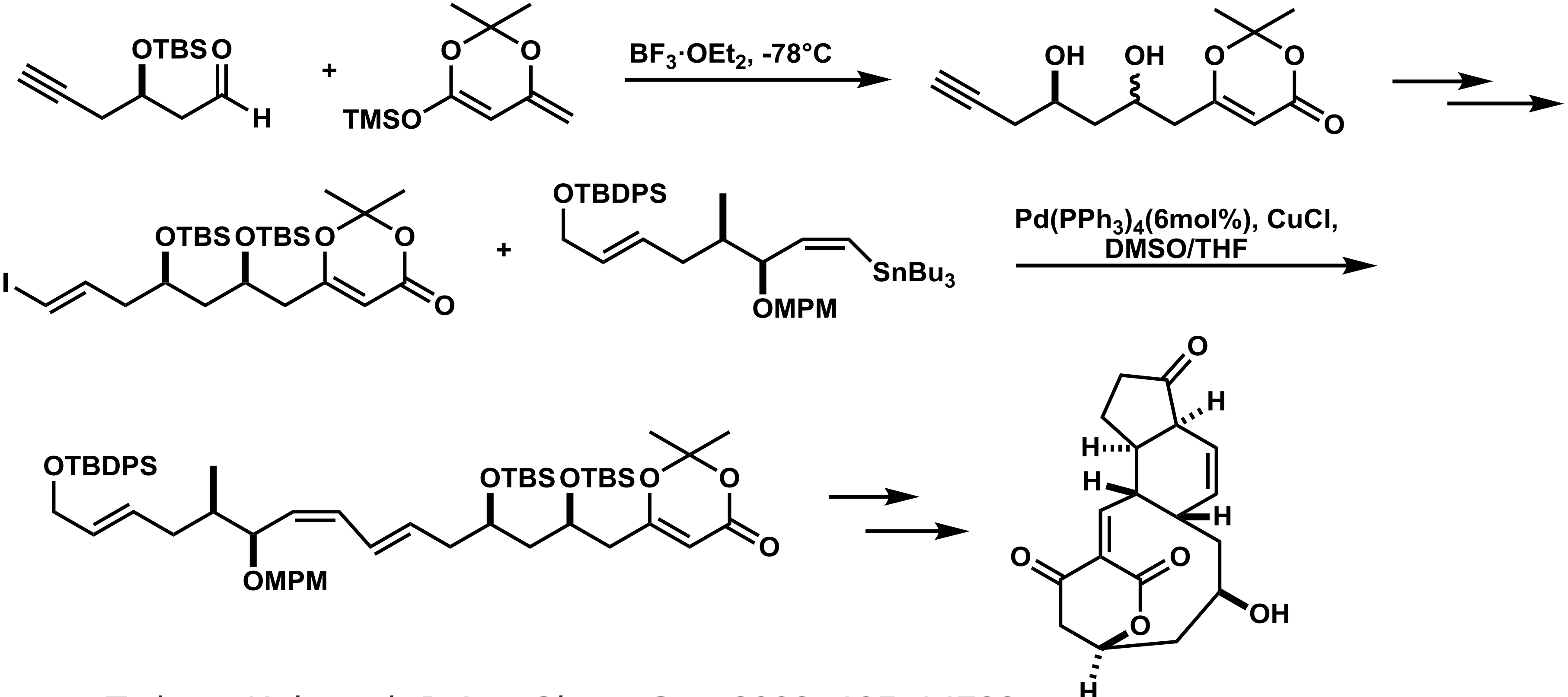
- 1. Acyclic Sillicon Dienolates
- Representative members of the acyclic $d_4$ silyl butadiene family



# Diastereoselective and Unselective Processes

## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 1. Acyclic Sillicon Dienolates
- Total Synthesis of (+)-Macquarimicin A

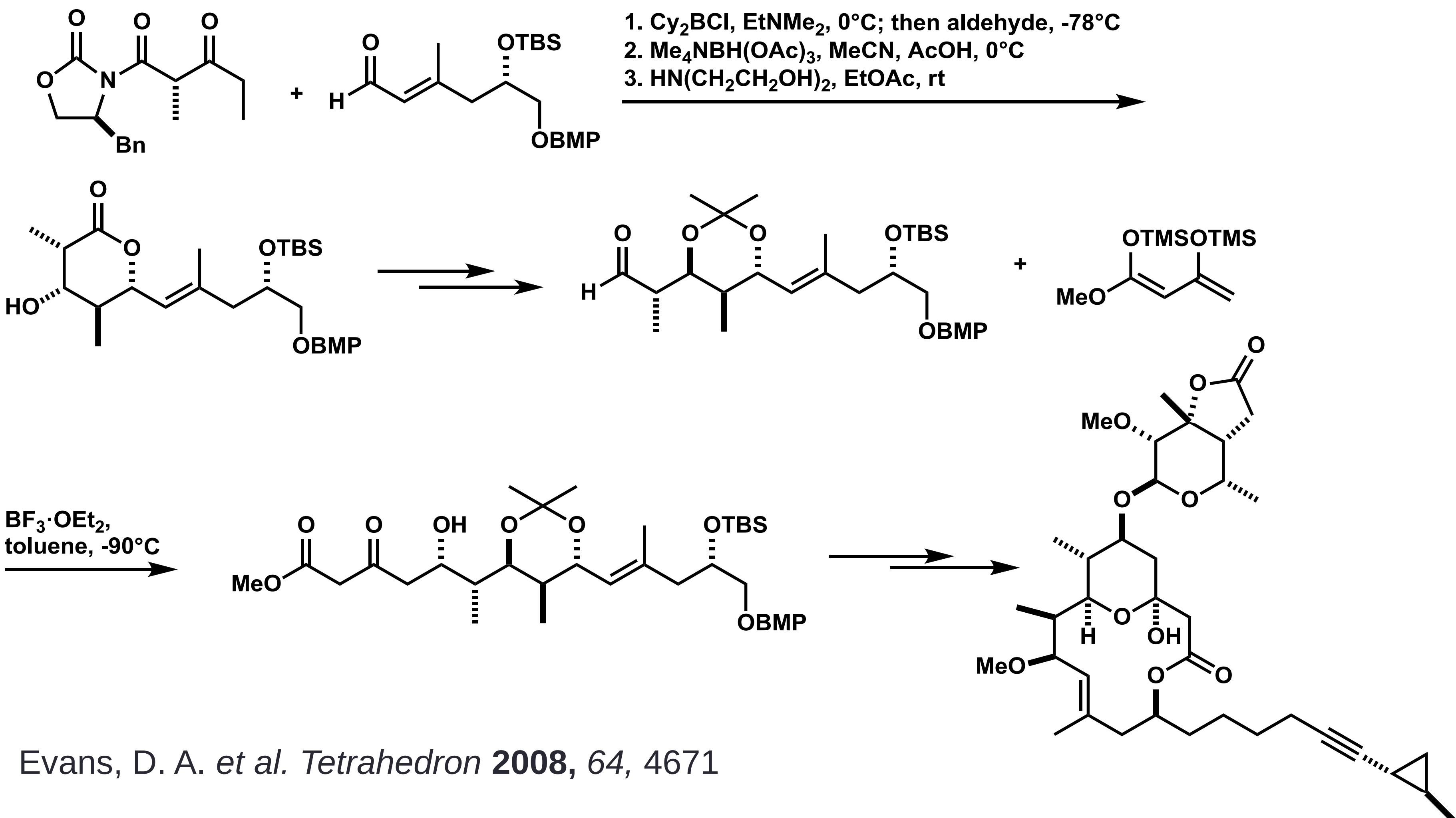



Tadano, K.-i. *et al. J. Am. Chem. Soc.* **2003**, *125*, 14722
Tadano, K.-i. *et al. J. Am. Chem. Soc.* **2004**, *126*, 11254

# Diastereoselective and Unselective Processes

## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 1. Acyclic Sillicon Dienolates
- Total synthesis of (-)-Callipeltoside A

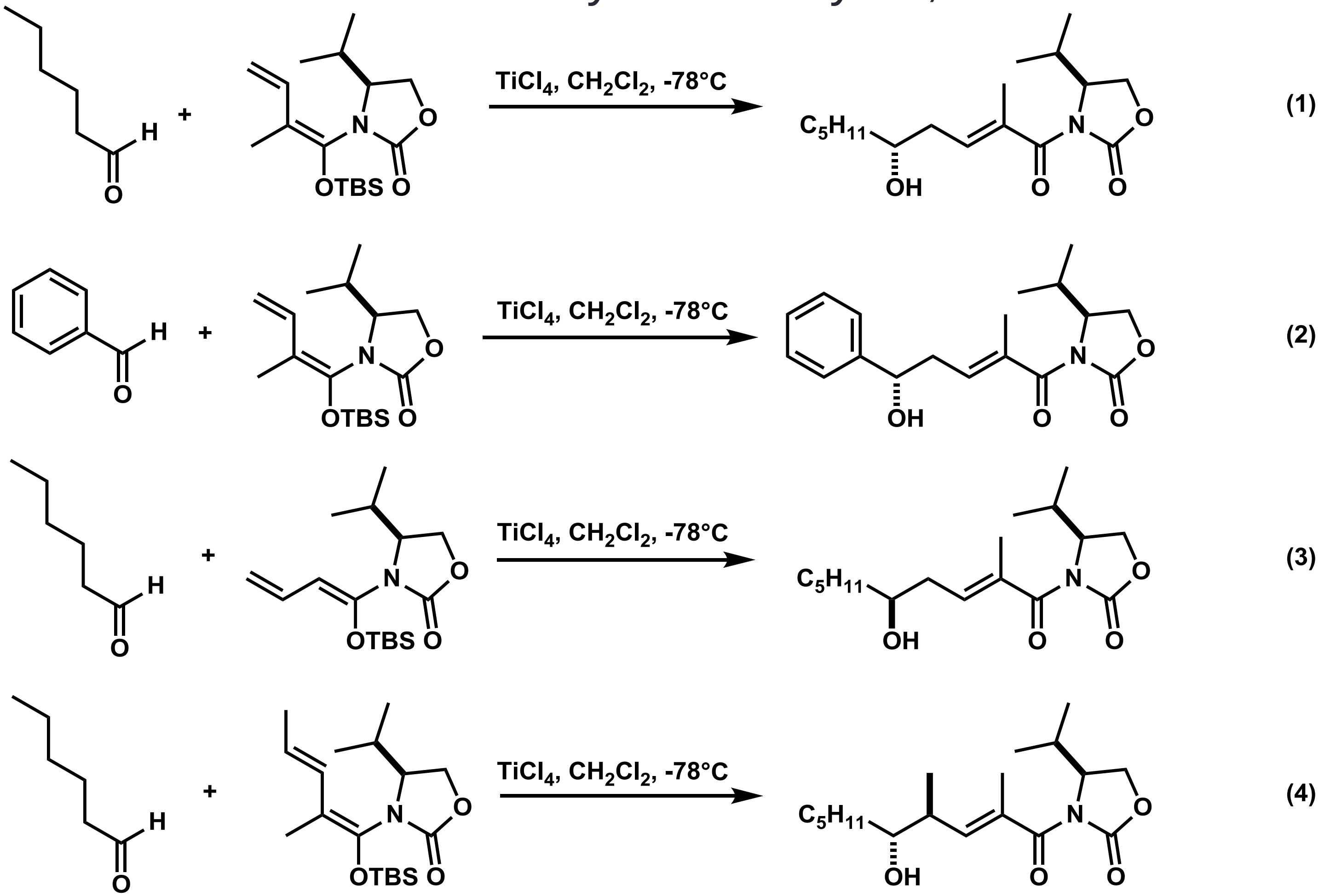



Evans, D. A. *et al. Tetrahedron* **2008,** *64,* 4671

# Diastereoselective and Unselective Processes

## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

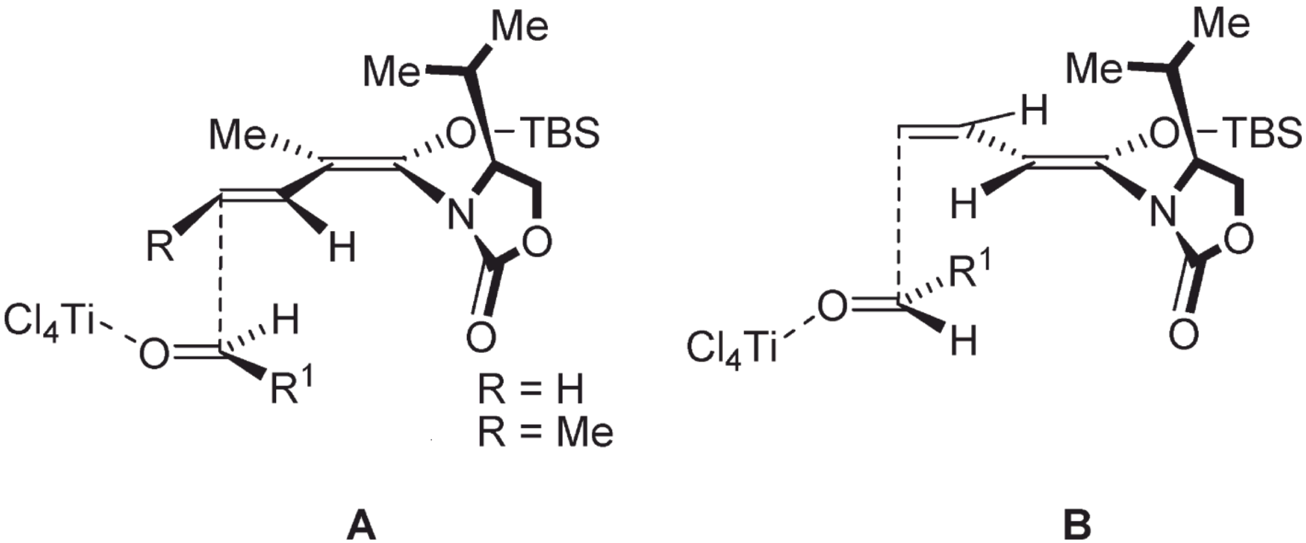
- 1. Acyclic Sillicon Dienolates
- VMAR addition with chiral vinylketene silyil N,O-acetal




Kobayashi, S. *et al.* *J. Am. Chem. Soc*. **2004,** *126*, 13604

# Diastereoselective and Unselective Processes
## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 1. Acyclic Sillicon Dienolates



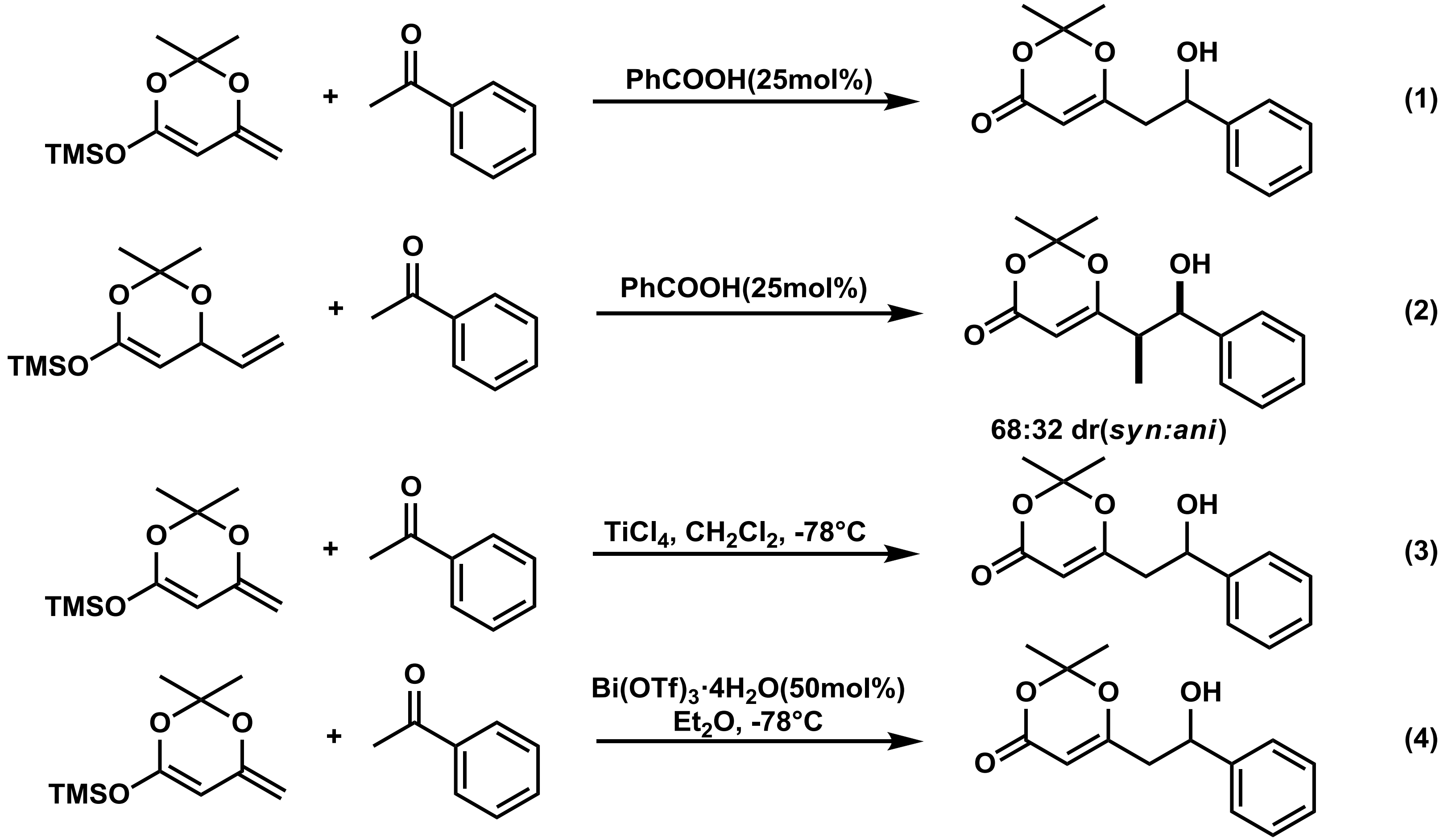

Proposed transition state models for the $TiCl_4$-promoted VMAR involving α-methyl vinyl ketene *N*,*O*-acetals (A) or unsubstituted vinyl ketene *N*,*O*-acetals (B).

Kobayashi, S. *et al. J. Am. Chem. Soc.* **2004,** *126*, 13604

# Diastereoselective and Unselective Processes

## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

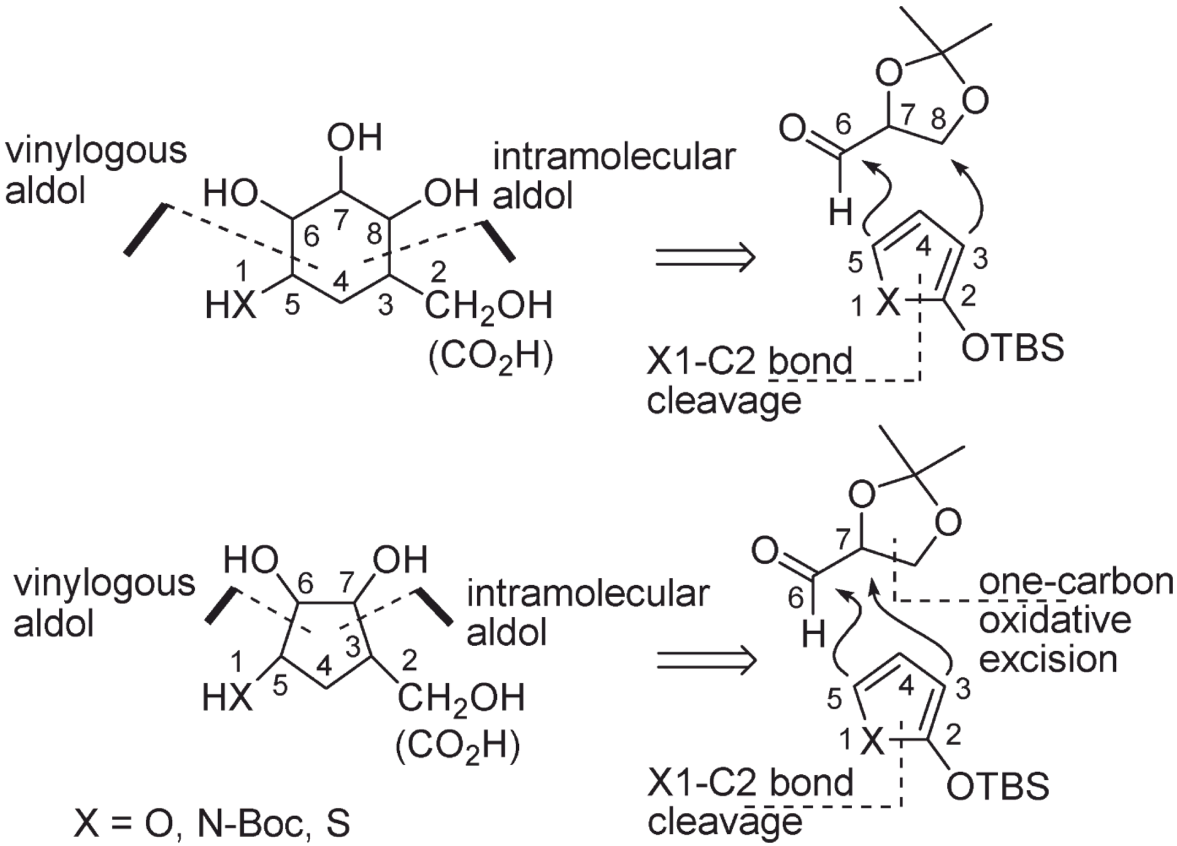
- 1. Acyclic Sillicon Dienolates
- Bronsted acid-promoted VMAR to racemic product




Scettri, A. *et al. Tetrahedron Lett.* **2005**, *46,* 6141 Kirsch, S. *et al. Synlett* **2001,** *1974*
Wischert, R. *Tetrahedron Lett.* **2006,** *47*, 9089

# Diastereoselective and Unselective Processes
## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 2.Cycic Silicon Dienolates
- First-generation strategy towards cyclohexane and cyclopentane polyols

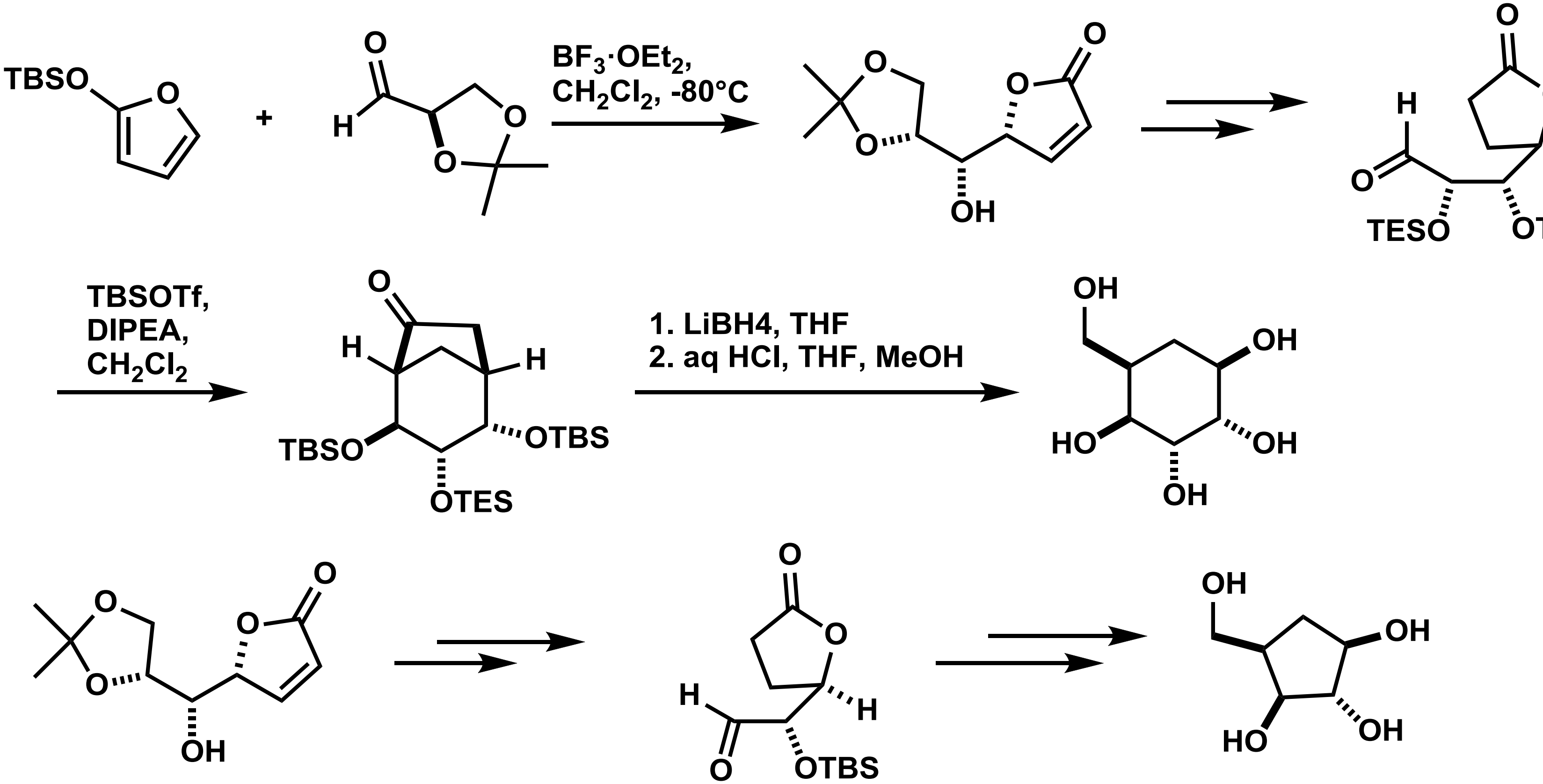



Casiraghi, G. *et al. Mini-Rev. Org. Chem.* **2004**, *1*, 343

# Diastereoselective and Unselective Processes

## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 2.Cycic Silicon Dienolates
- Diastereoselective synthesis of 5a-carbapyranose and 4a-carbafuranose



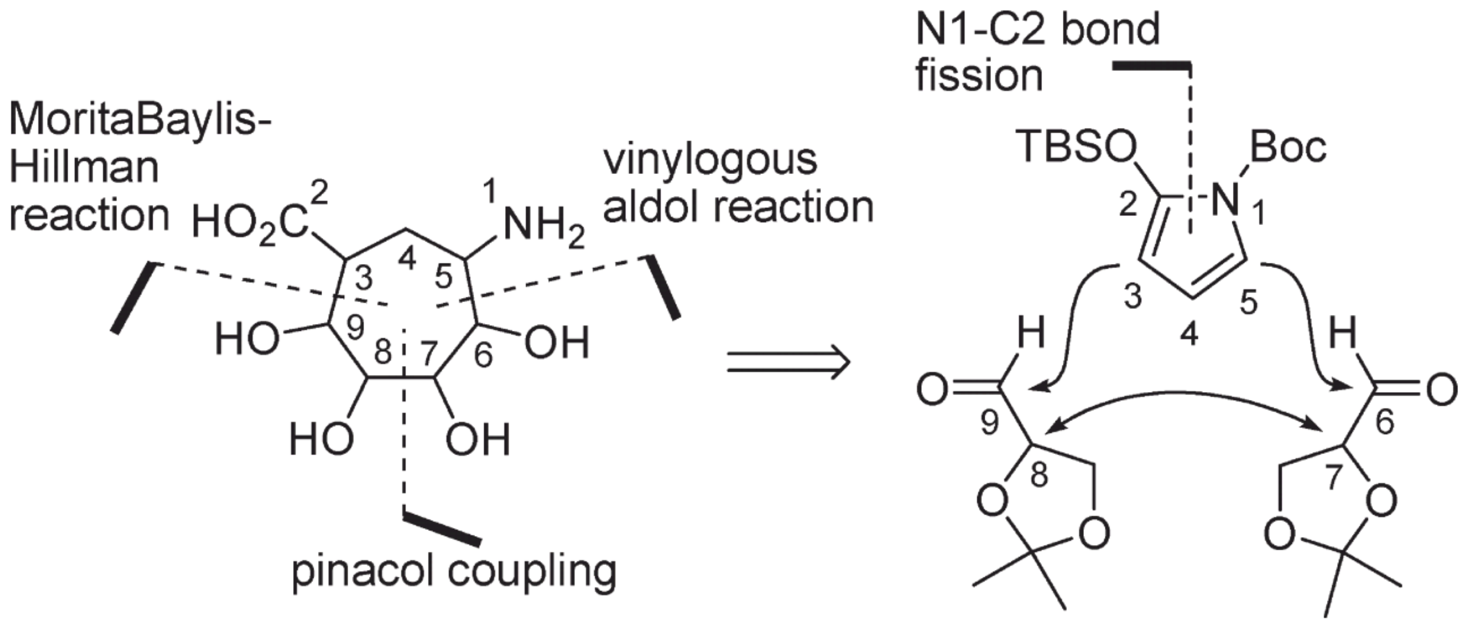

(1)

(2)

(1) Casiraghi, G. *et al. Eur. J. Org. Chem*. **2002**, 1956
(2) Casiraghi, G. *et al. J. Org. Chem*. **2001**, *66,* 8070

# Diastereoselective and Unselective Processes
## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 2.Cycic Silicon Dienolates
- Second-generation strategy to amino acid polyols

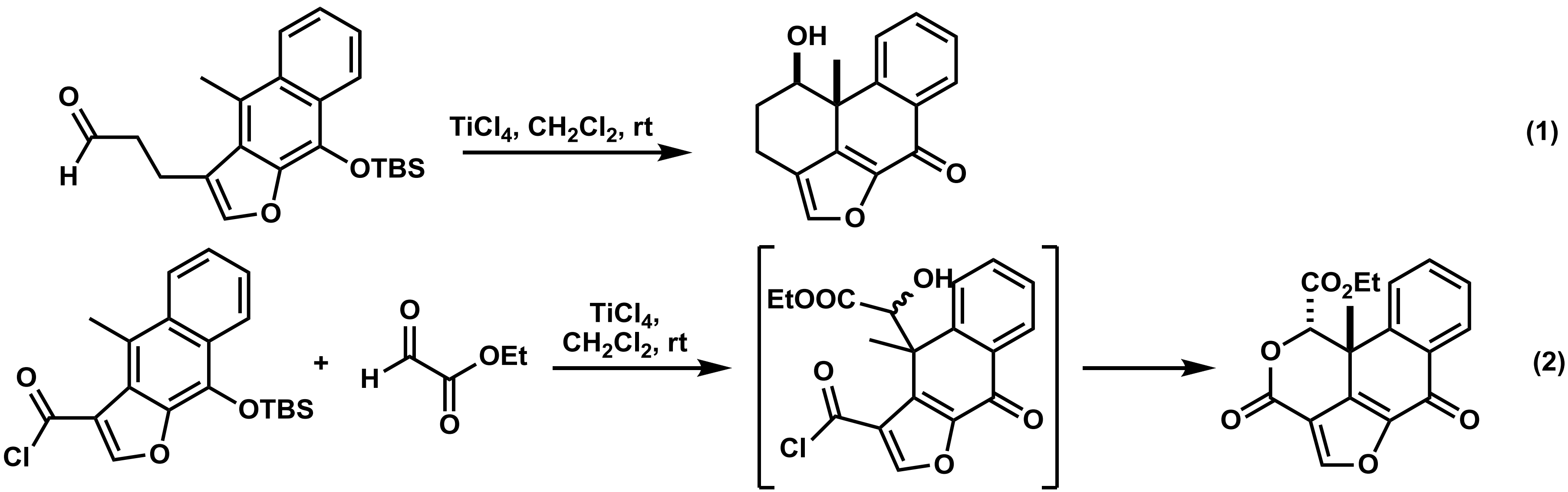



Casiraghi, G. *et al. J. Org. Chem*. **2006**, *71,* 225

# Diastereoselective and Unselective Processes

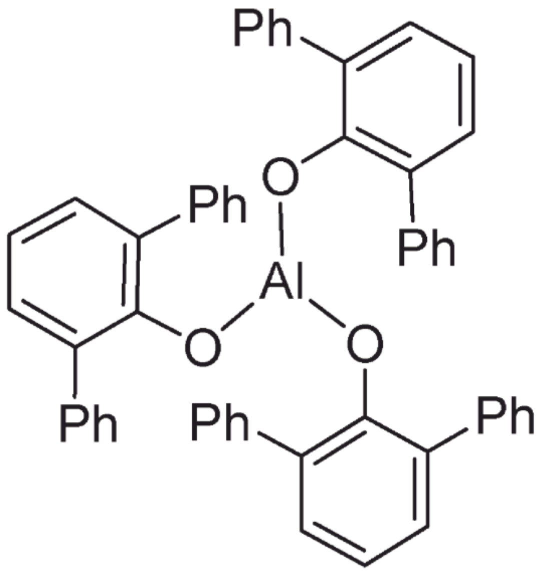
## Indirect, Mukaiyama Type Addition of Sillcon Dienolates

- 2.Cycic Silicon Dienolates
- Phenylogous aldol moves during the synthesis of Viridin/Wortmannin models

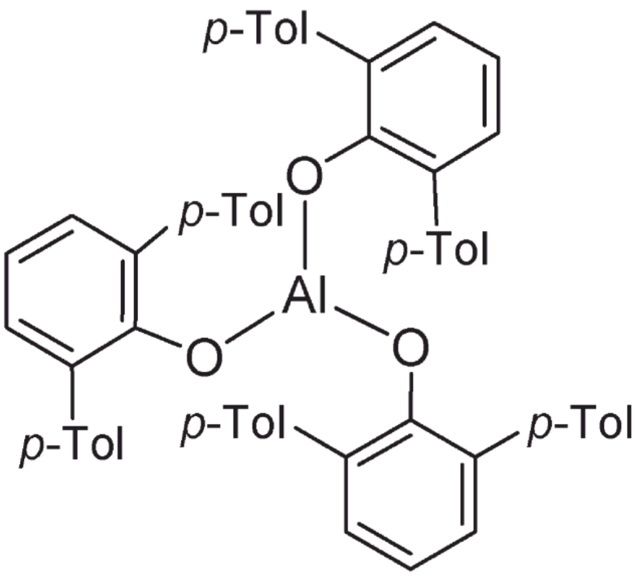



Sessions, E. H. *et al. Org. Lett.* **2006,** *8,* 4125
Sessions, E. H. *et al. Org. Lett.* **2007,** *9,* 3221

# Diastereoselective and Unselective Processes
## Direct Addition of in situ-Gerenated Dienolates



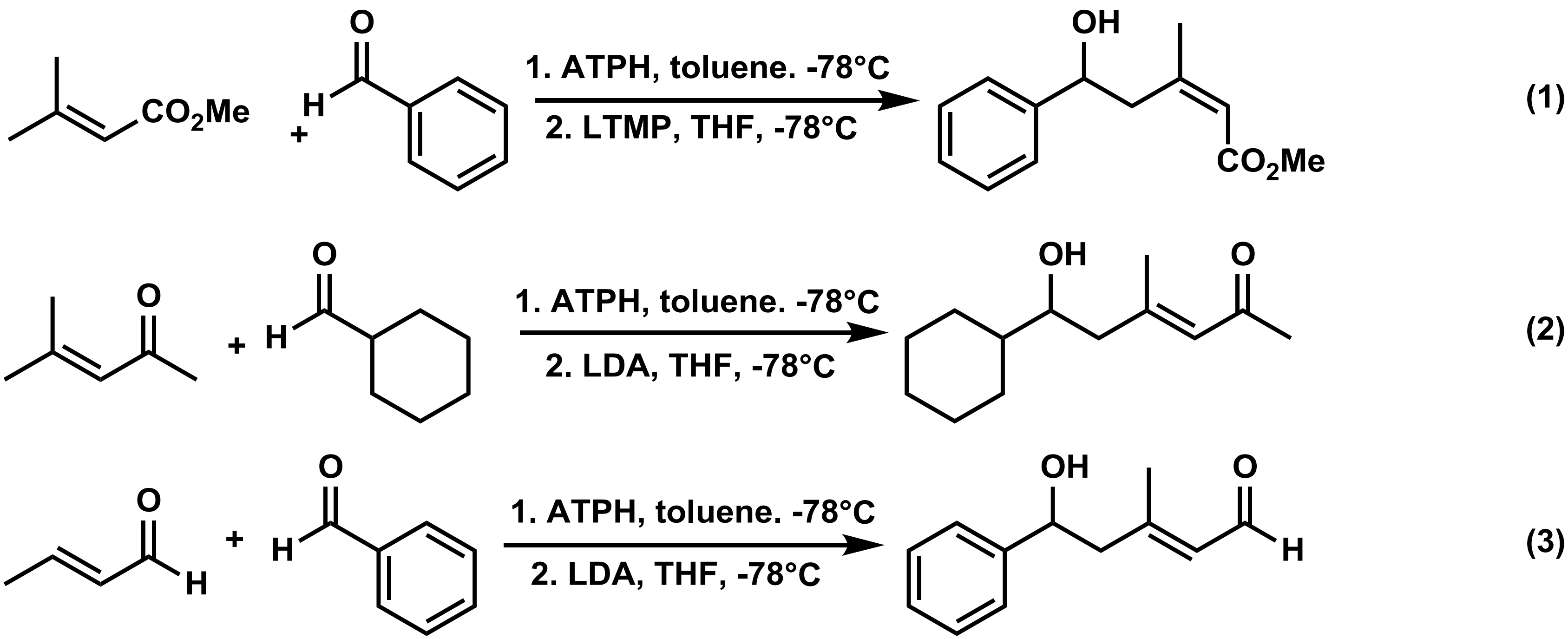

ATPH




Me-ATPH

# Diastereoselective and Unselective Processes
## Direct Addition of in situ-Gerenated Dienolates

- Aldolization of α,β-unsaturated carbonyl compounds with aldehydes using ATPH



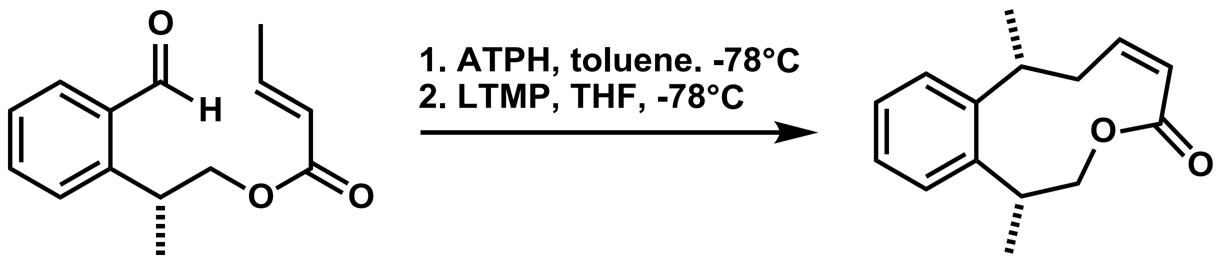

γ-regioselective
High *Z/E* selective

Yamamoto, H. *et al. J. Am. Chem. Soc*. **2003**, *125,* 6200

# Diastereoselective and Unselective Processes
## Direct Addition of in situ-Gerenated Dienolates

- Application of inter- and intramolecular Yamamoto VAR


(1)



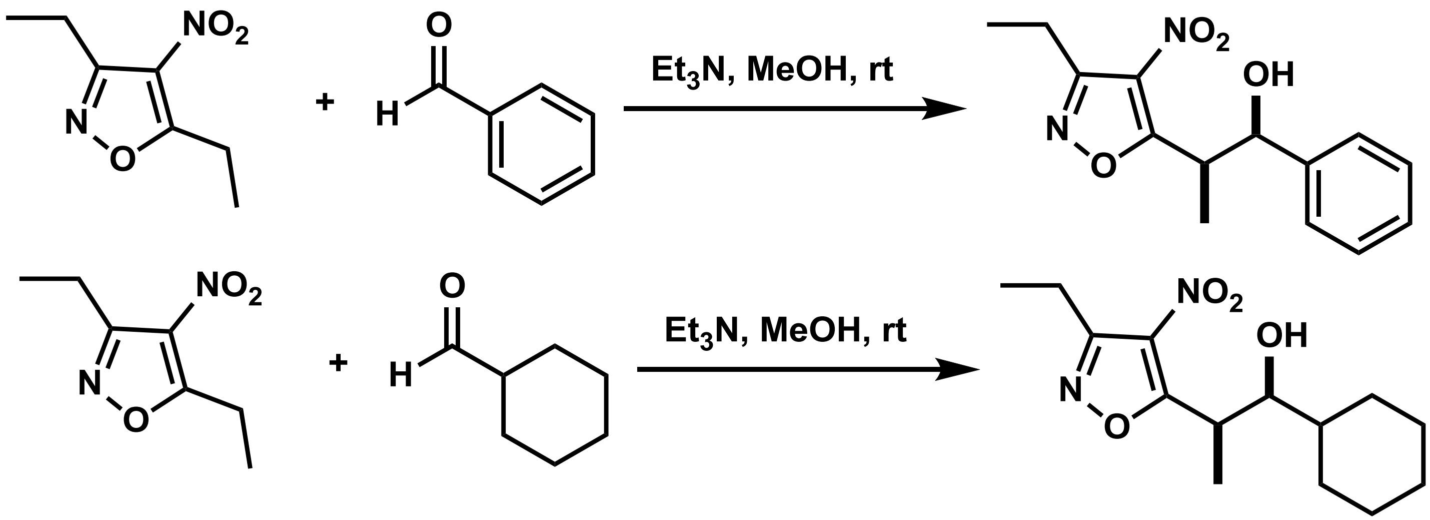

(2)

(1) Marquez, R. *et al. Angew. Chem. Int. Ed.* **2001,** *40*, 603
(2) Sammakia, T. *et al. Org. Lett.* **2007,** *9,* 2103

# Diastereoselective and Unselective Processes

## Direct Addition of in situ-Gerenated Dienolates

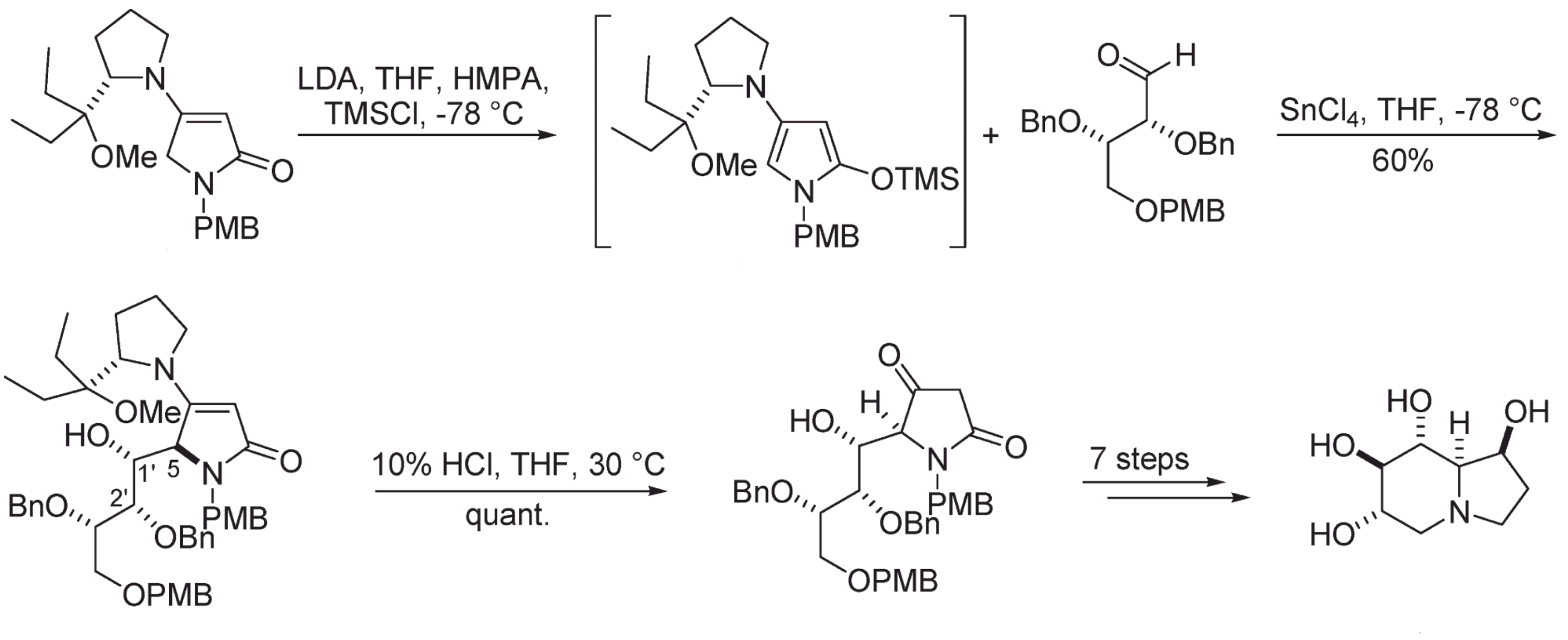
- Direct vinylogous nitroaldol (Henry) reaction using nitroisoxazole




Suresh, S. *et al. Org. Lett.* **2007,** *9,* 2103

# Diastereoselective and Unselective Processes
## Direct Addition of in situ-Gerenated Dienolates

- Total synthesis of (+)-Castanospermine featuring a diasteteoselective direct VAR



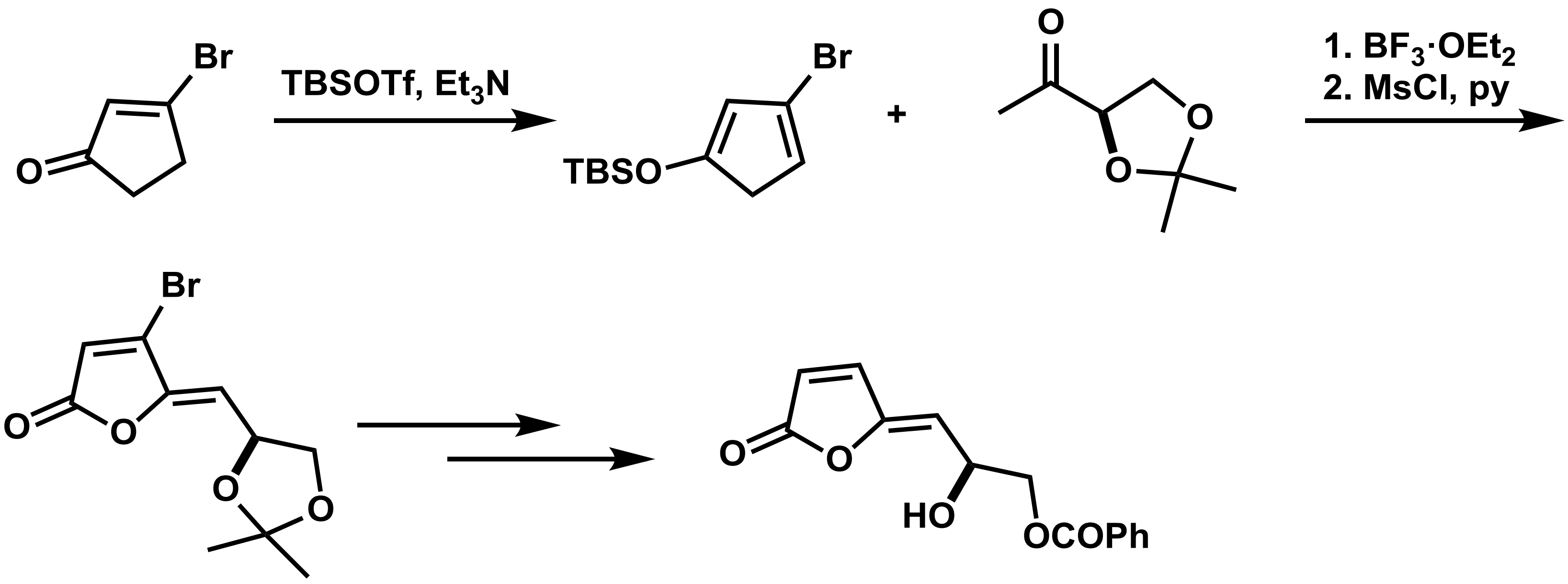

99.5:0.5 dr

(+)-castanospermine

Huang, P.-Q. *et al. Tetrahedron Lett.* **2008**, *49*, 383
Huang, P.-Q. *et al. Eur. J.* **2010**, *16,* 5755

# Diastereoselective and Unselective Processes
## Direct Addition of in situ-Gerenated Dienolates

- Synthesis of (*S*)-Melodorinol

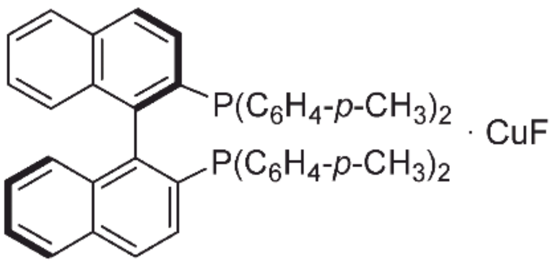



Pouliot, M. *et al. Synlett* **2007,** 219

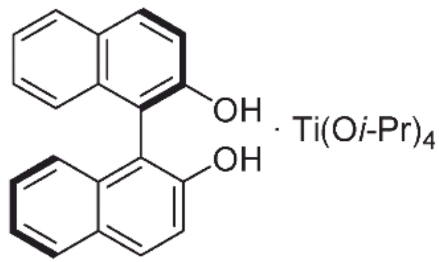
# Enantioselective Processes

## Indirect, Mukaiyama type additions of silicon dienolates

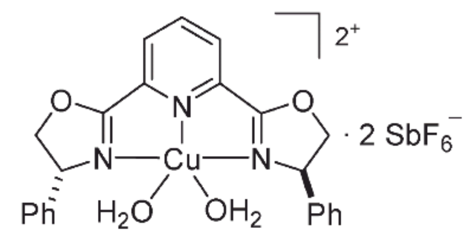
- 1. Acyclic Silicon Dienolates
- Repersentative metal-based chiral nonracemic complexes used in catalytic enantioselective VMAR



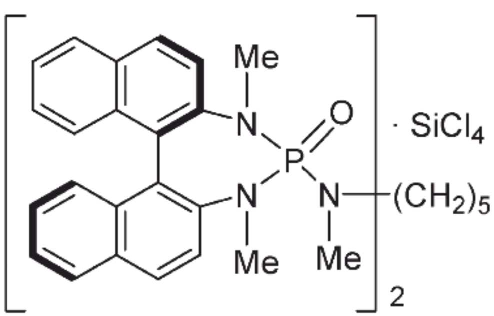

**A**
(*R*)-TolBINAP·CuF



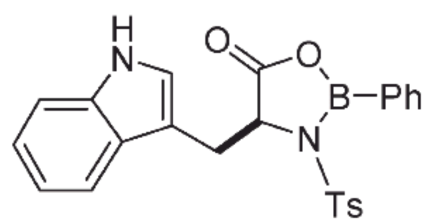

**B**
(*R*)-BINOL·Ti(O*i*-Pr)$_4$



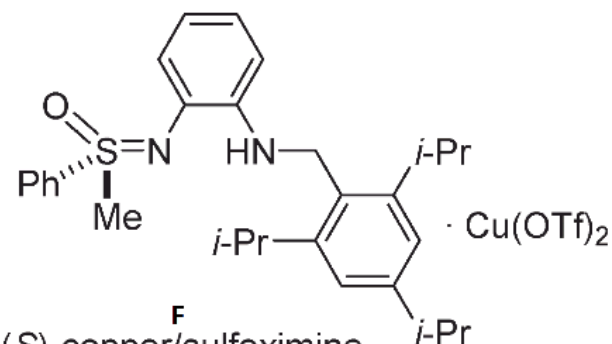

**C**
[Cu(*R*,*R*)PhPyBox](SbF$_6$)$_2$·2H$_2$O




**D**
(*R*,*R*)-bisphosphoramide·SiCl$_4$




**E**
(*S*)-OBX

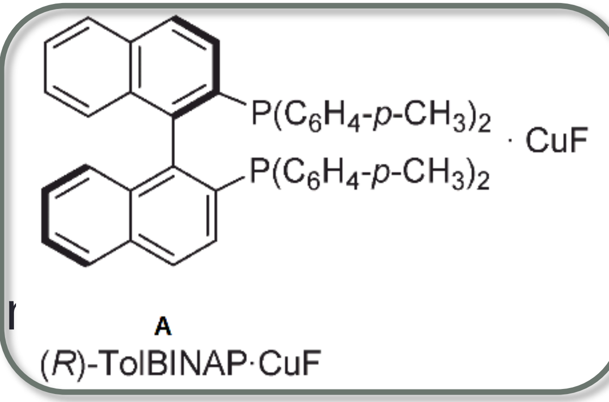


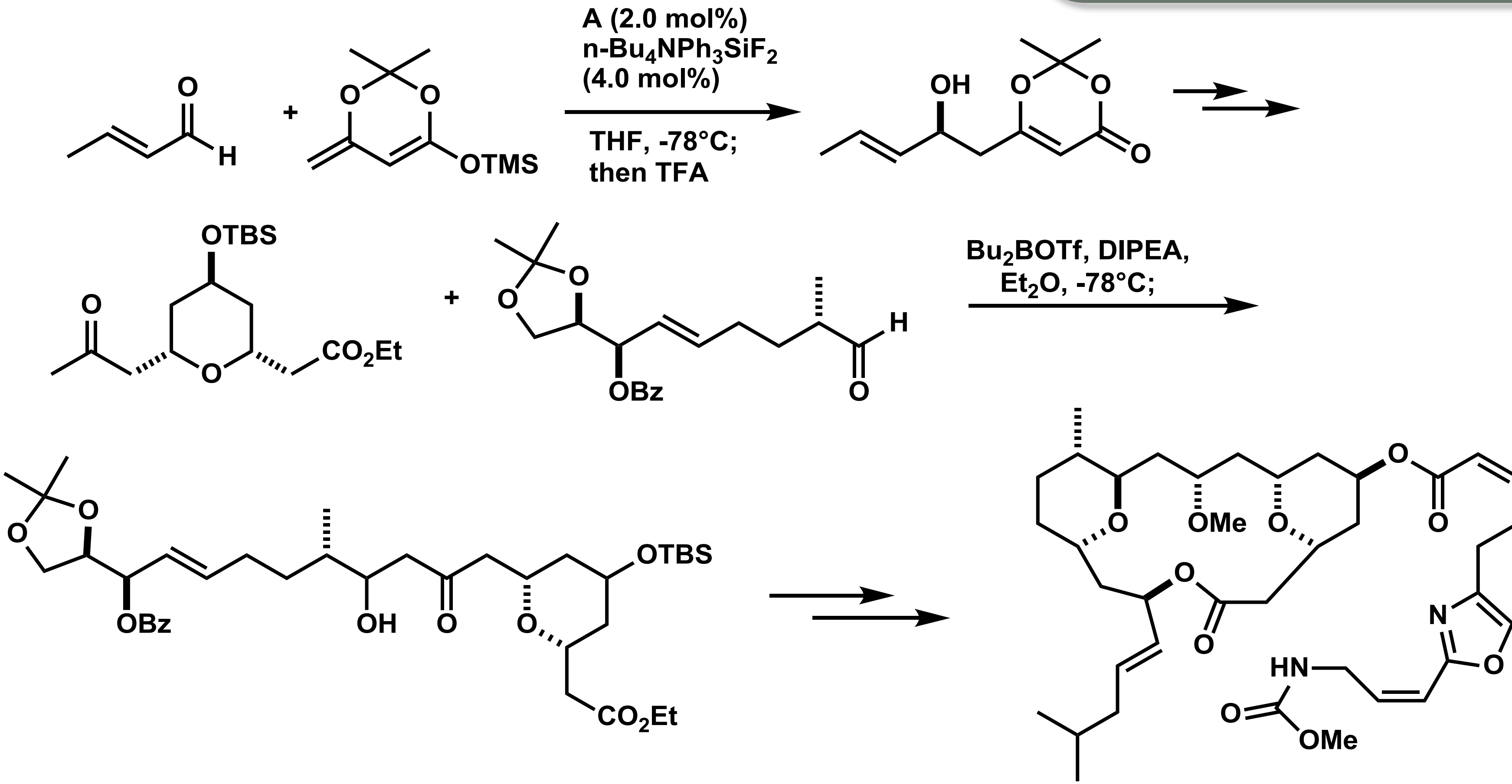

**F**
(*S*)-copper/sulfoximine

# Enantioselective Processes

## Indirect, Mukaiyama type additions of

- 1. Acyclic Silicon Dienolates
- Total synthesis of C1-C22 macrolactone fragmer

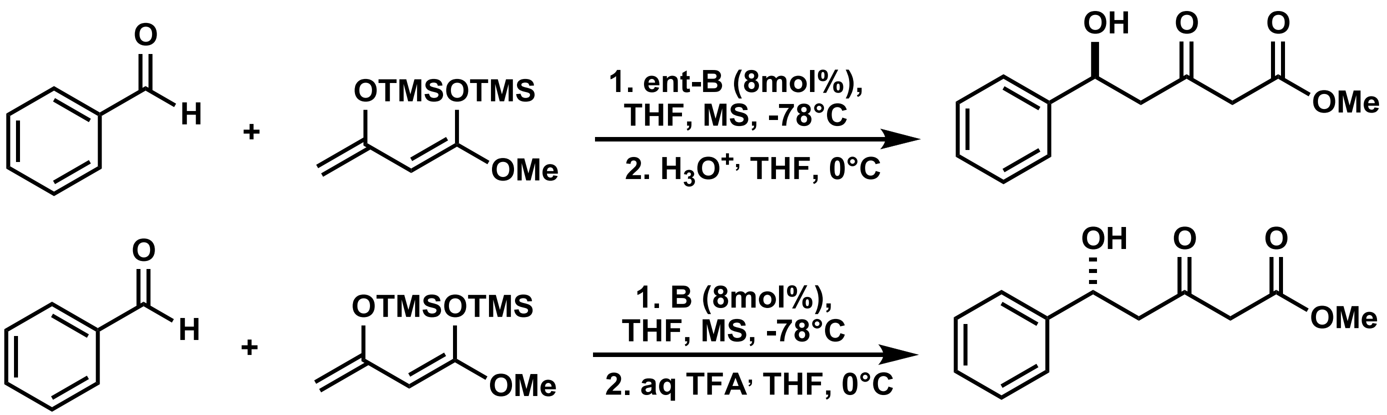



Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2002,** *41*, 4098

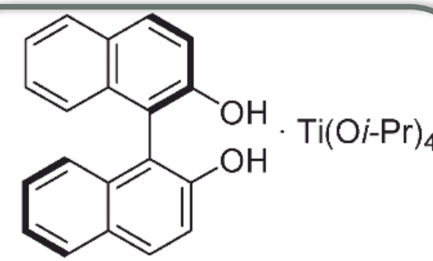
# Enantioselective Processes
## Indirect, Mukaiyama type additions of silicon dienolates

- 1. Acyclic Silicon Dienolates
- Asymmetric VMAR addition involving Chan diene




(1)

(2)



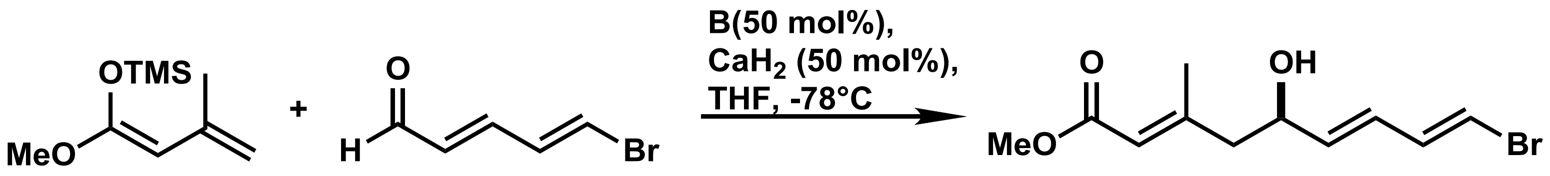

**B**

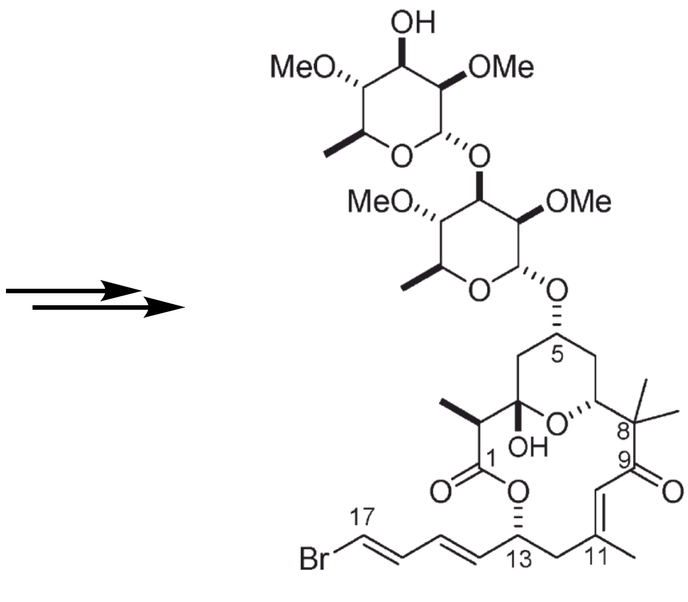
($R$)-BINOL·Ti(O$i$-Pr)$_4$

(1) Scettri, A. *et al.* *Tetrahedron:Asymmetry* **20000,** *11,* 2255
(2) Scettri, A. *et al.* *Tetrahedron:Asymmetry* **20001,** *12,* 959

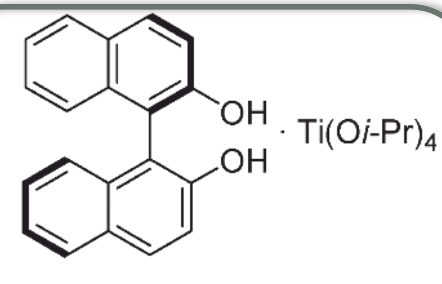
# Enantioselective Processes
## Indirect, Mukaiyama type additions of silicon dienolates

- 1. Acyclic Silicon Dienolates
- Optimized enantioselective VMAR in the total synthesis of (-)-auriside A




(-)-auriside A



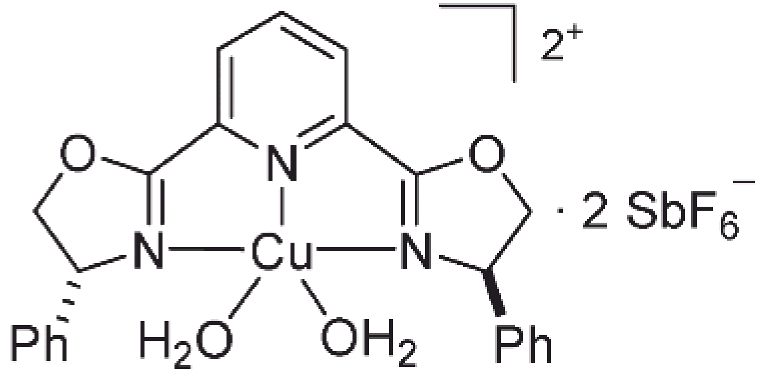

**B**

(*R*)-BINOL·Ti(O*i*-Pr)$_4$

Mackay, A. C. *et al. Angew. Chem. Int. Ed.* **2005,** *44,* 1130

# Enantioselective Processes
## Indirect, Mukaiyama type additions of silicon dienolates

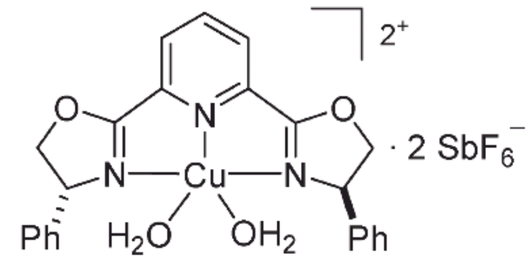
- 1. Acyclic Silicon Dienolates




c

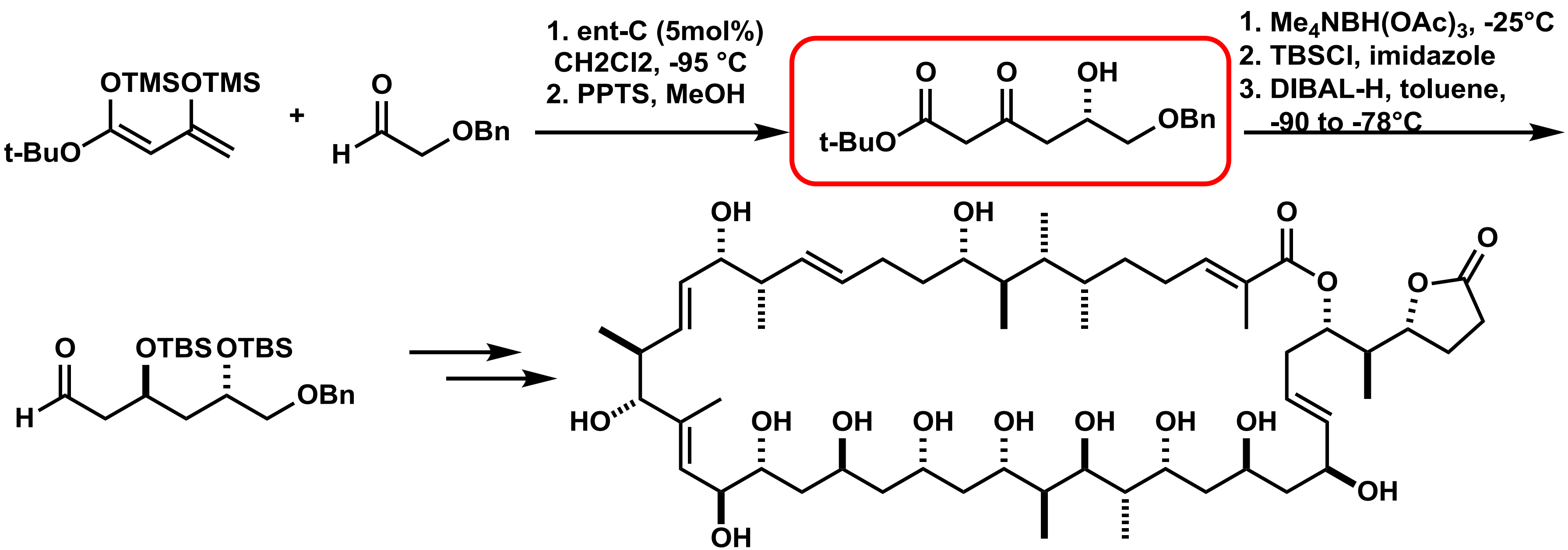
[Cu(*R*,*R*)PhPyBox]$(SbF_6)_2 \cdot 2H_2O$

# Enantioselective Processes
## Indirect, Mukaiyama type additions o




C
$[Cu(R,R)PhPyBox](SbF_6)_2{\cdot}2H_2O$

- 1. Acyclic Silicon Dienolates
- Enantioselective synthesis of fragment via VM… acidic Copper( II )-PyBox complex *ent*-C

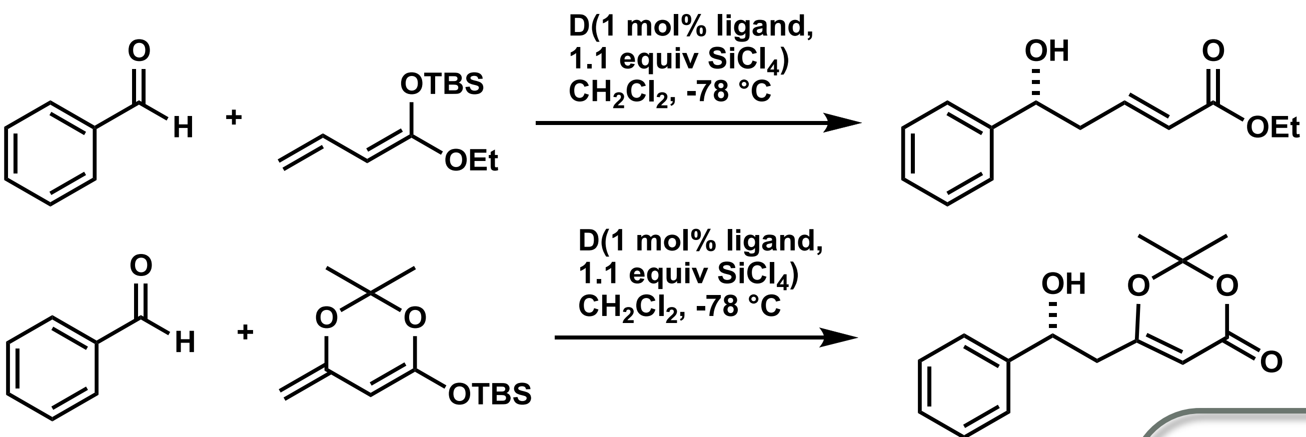



Evans, D. A. *et al. Angew. Chem. Int. Ed*. **2007,** *46*, 541

# Enantioselective Processes

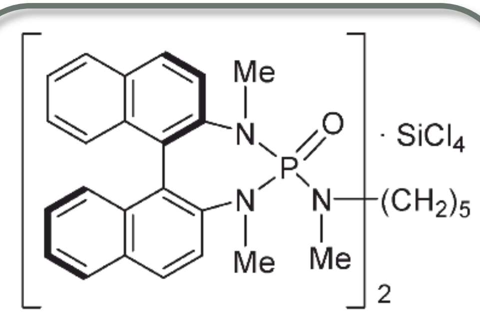
## Indirect, Mukaiyama type additions of silicon dienolates

- 1. Acyclic Silicon Dienolates
- Biophosphoramide-catalyzed enantioselective VMAR of easter- or dioxinone-derived silyl dienol ethers




(1)

(2)




**D**

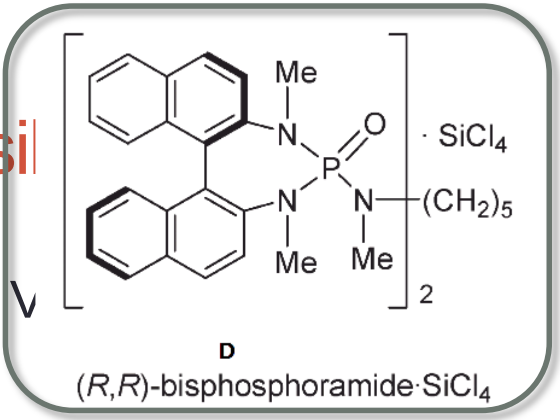
(*R*,*R*)-bisphosphoramide·$SiCl_4$

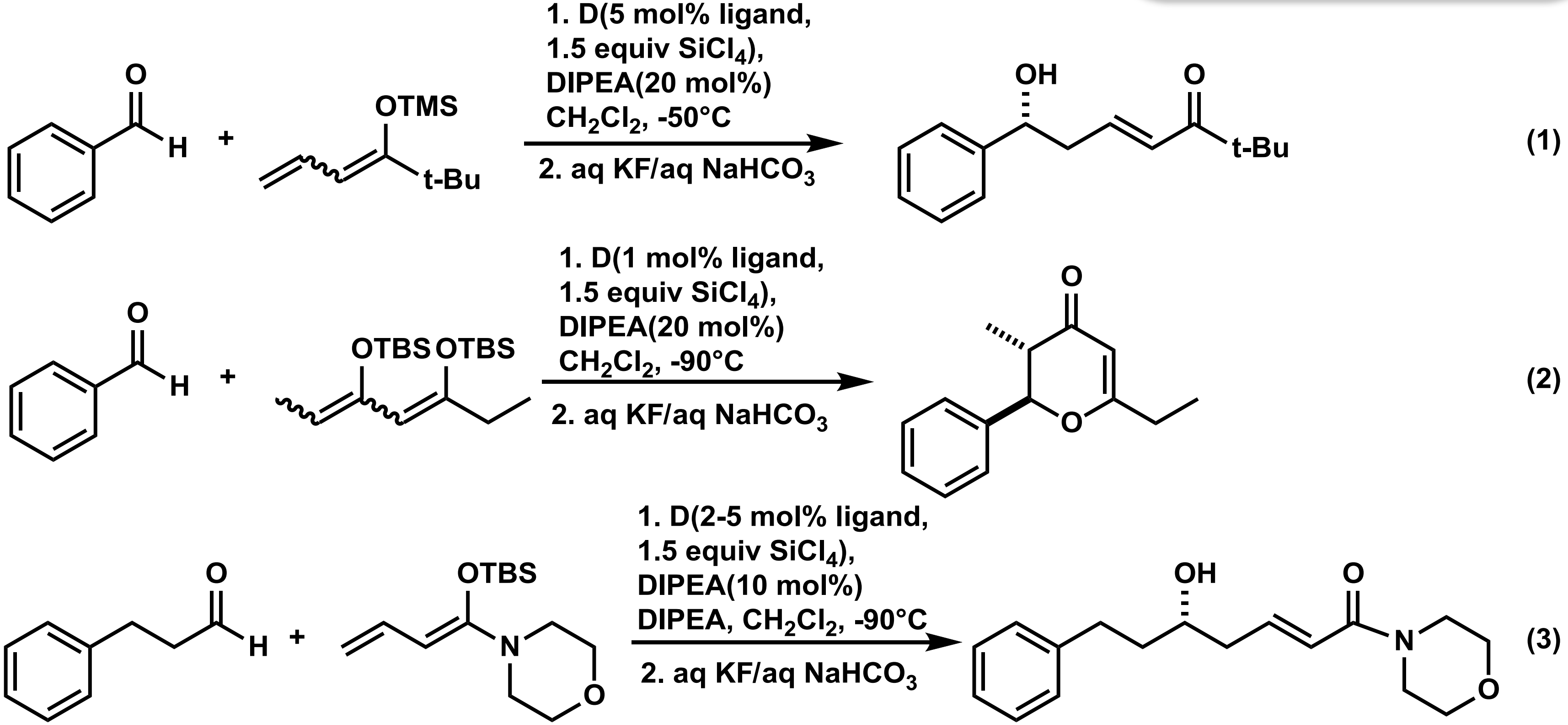
(1) Denmark, S. E. *et al. J. Am. Chem. Soc*. **2003,** *125,* 7800
(2) Denmark, S. E. *et al. J. Am. Chem. Soc*. **2005,** *127,* 3774

# Enantioselective Processes

## Indirect, Mukaiyama type additions of sil

- 1. Acyclic Silicon Dienolates
- Biophosphoramide-catalyzed enantioselective V diketone, or amide-derived silyl dieolates



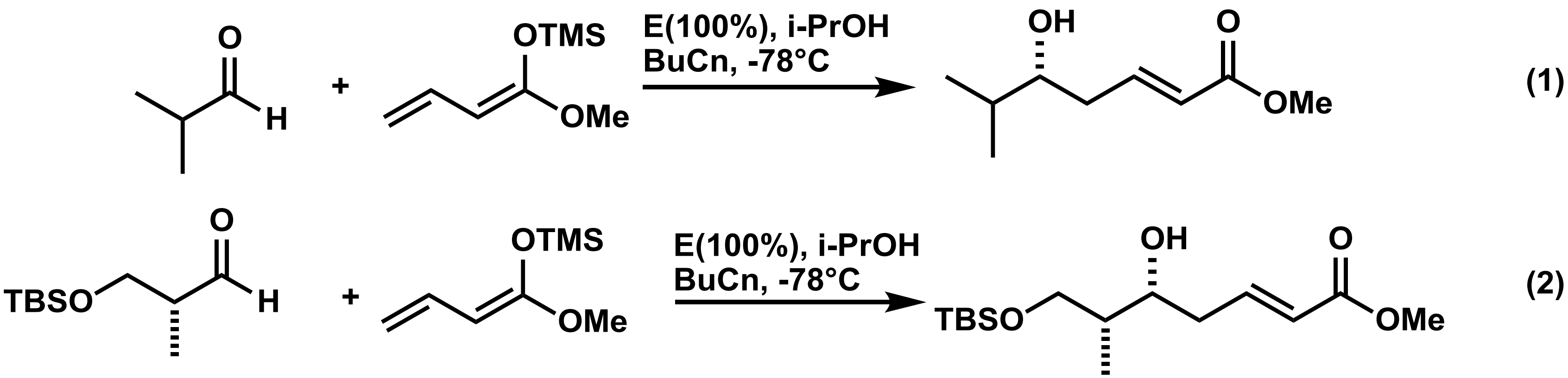



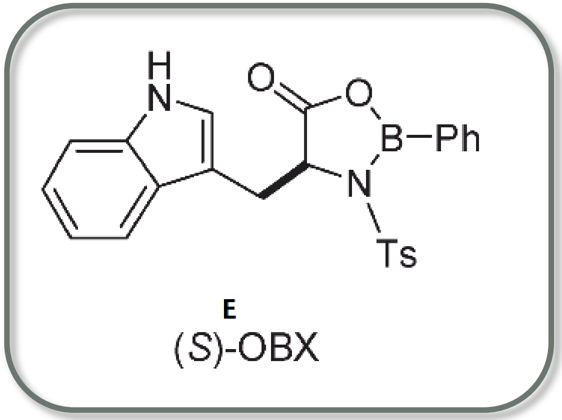

Denmark, S. E. *et al. J. Am. Chem. Soc.* **2005,** *127,* 8971

Denmark, S. E. *et al. J. Org. Chem*. **2007,** *72*, 5668

# Enantioselective Processes
## Indirect, Mukaiyama type additions of silicon dienolates

- 1. Acyclic Silicon Dienolates
- Use of chiral oxazaborolidine catalysts in asymmetric VMAR



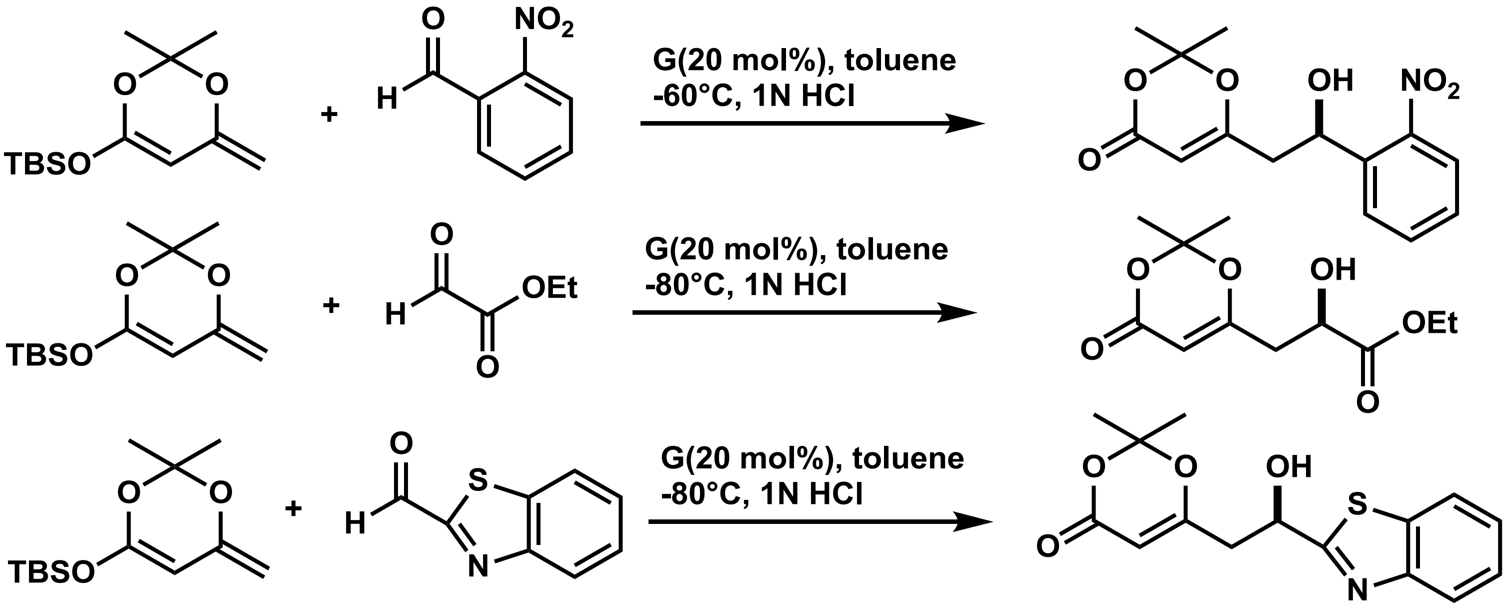



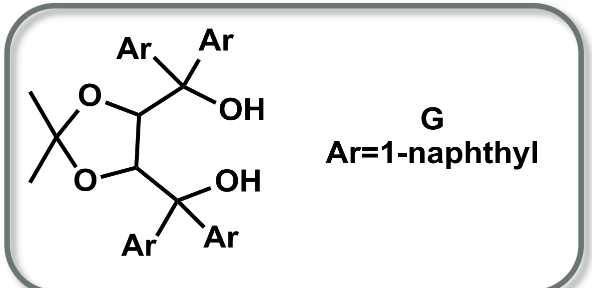

Simsek, S. *et al. Org. Lett.* **2007,** *9,* 5637

# Enantioselective Processes

## Indirect, Mukaiyama type additions of silicon dienolates

- 1. Acyclic Silicon Dienolates
- Hydrogen bond-catalyzed asymmetric VMAR of dioxinone and various aldehydes

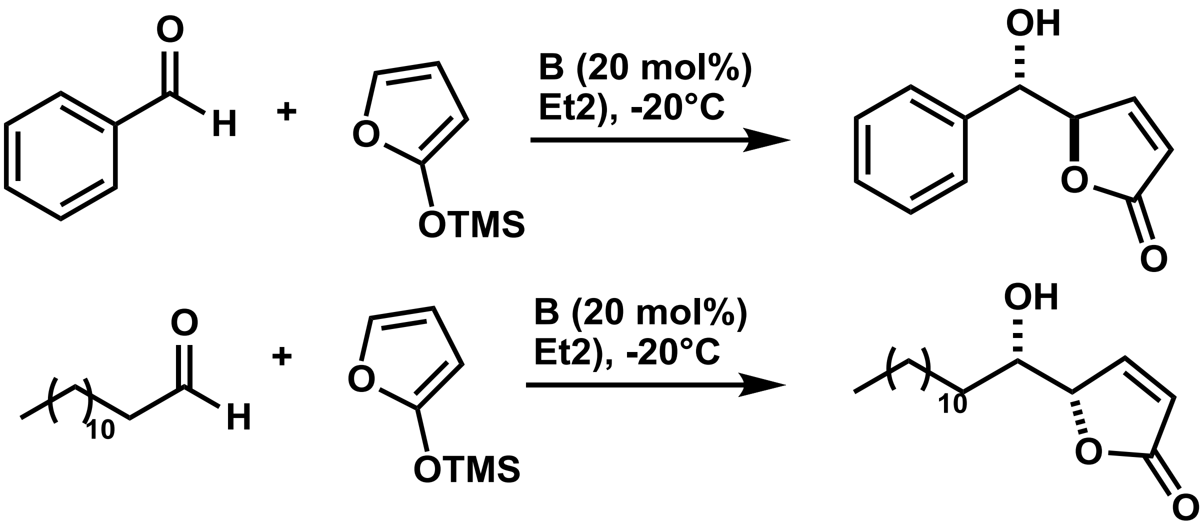


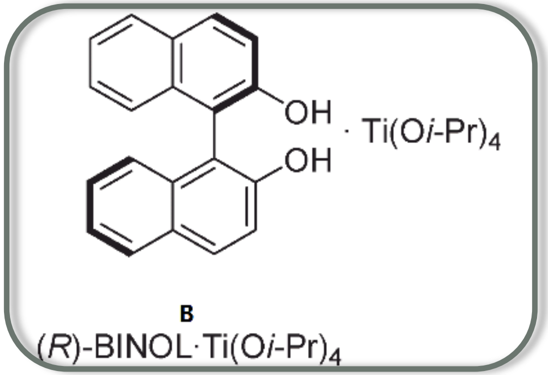




Rawal, V. H. *et al. Org. Lett*. **2005,** *7,* 5657

# Enantioselective Processes
## Indirect, Mukaiyama type additions of silicon dienolates

- 2. Cyclic Silicon Dienolates
- Ti(O*i*-Pr)$_4$/(R)-BINOL catalyzed VMAR of silyoxy furan

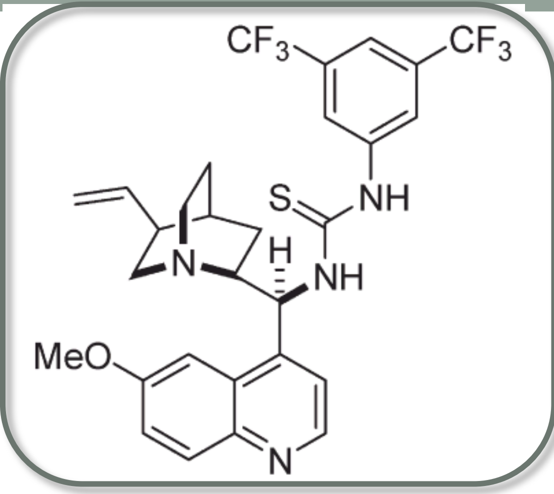


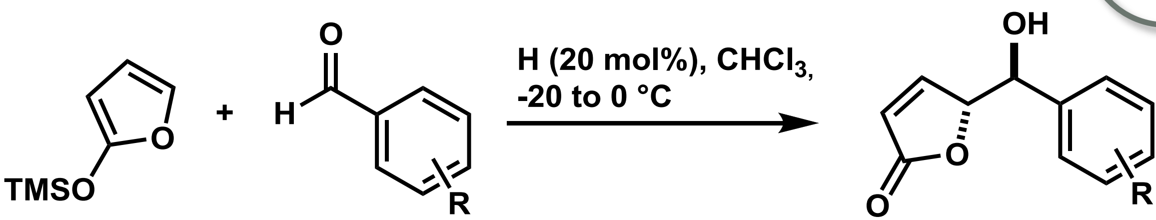



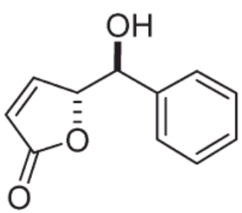

Szlosek, M. *et al. Heterocycles* **2000,** 52, 1005
Szlosek, M. *et al. Angew. Chem. Int. Ed*. **2000,** *39,* 1799

# Enantioselective Processes
## Indirect, Mukaiyama type additions of silic

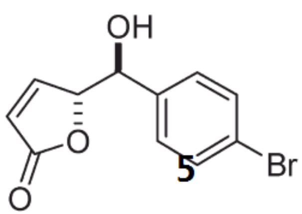
- 2. Cyclic Silicon Dienolates
- Enantioselective VMAR using quinine-thiourea c



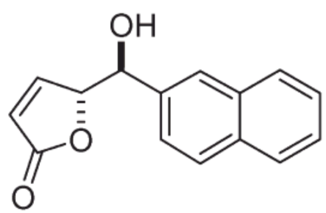



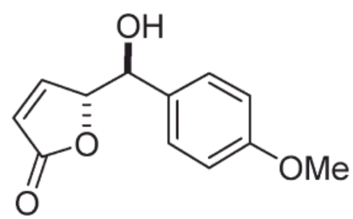

*anti-* **1**
78% yield;
89:11 dr (*anti:syn*);
86% ee (*anti*)



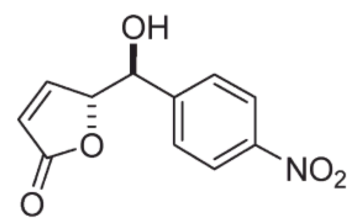

*anti-* **2**
75% yield;
88:12 dr (*anti:syn*);
84% ee (*anti*)




*anti-* **3**
90% yield;
90:10 dr (*anti:syn*);
89% ee (*anti*)




*anti-* **4**
72% yield;
60:40 dr (*anti:syn*);
82% ee (*anti*)

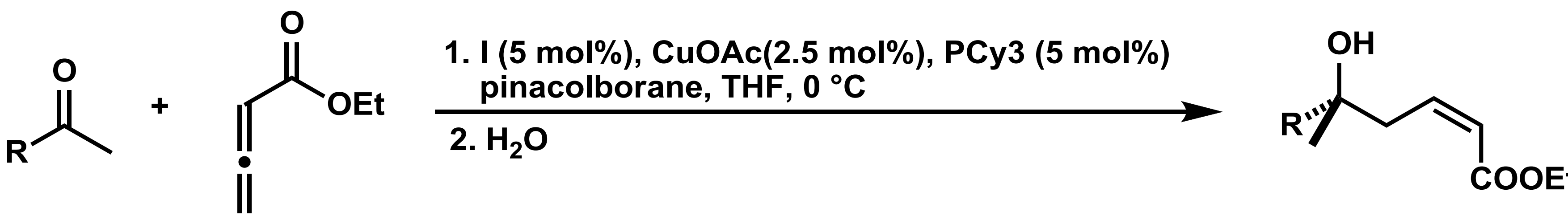


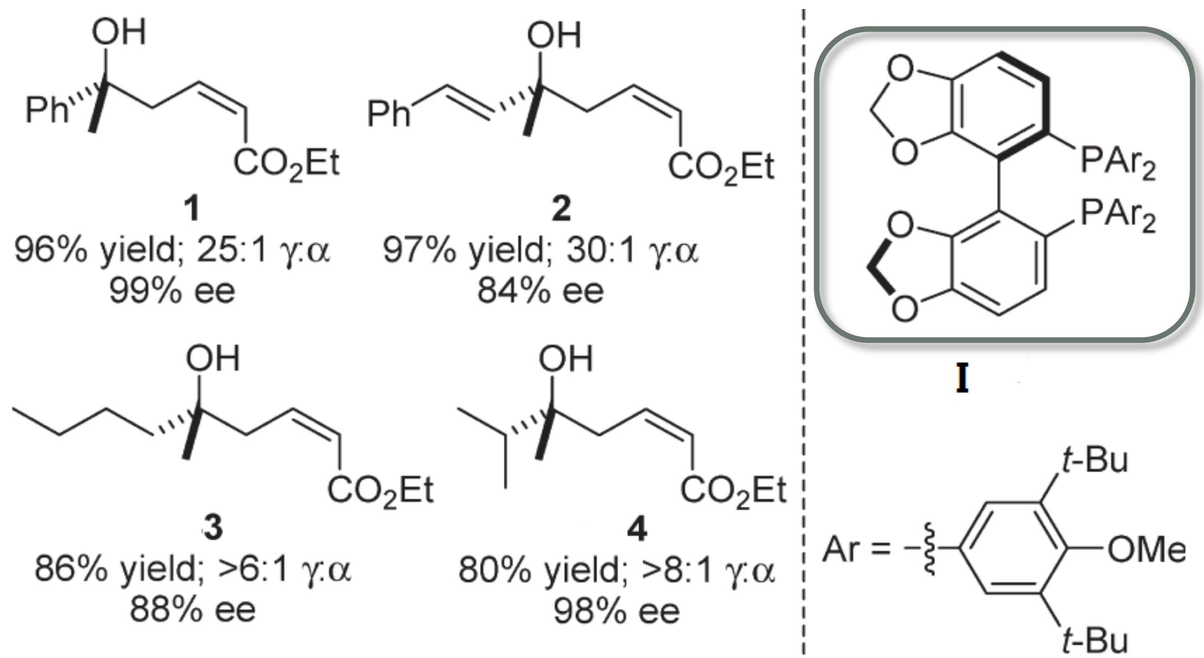

*anti-*
78% yield;
88:12 dr (*anti:syn*);
91% ee (*anti*)

Wang, W. *et al. Adv. Synth. Catal.* **2010,** *352,* 1291

# Enantioselective Processes
## Direct addition of in situ-generated dienolates

- Asymmetric reductive VAR of allenic esters to ketones



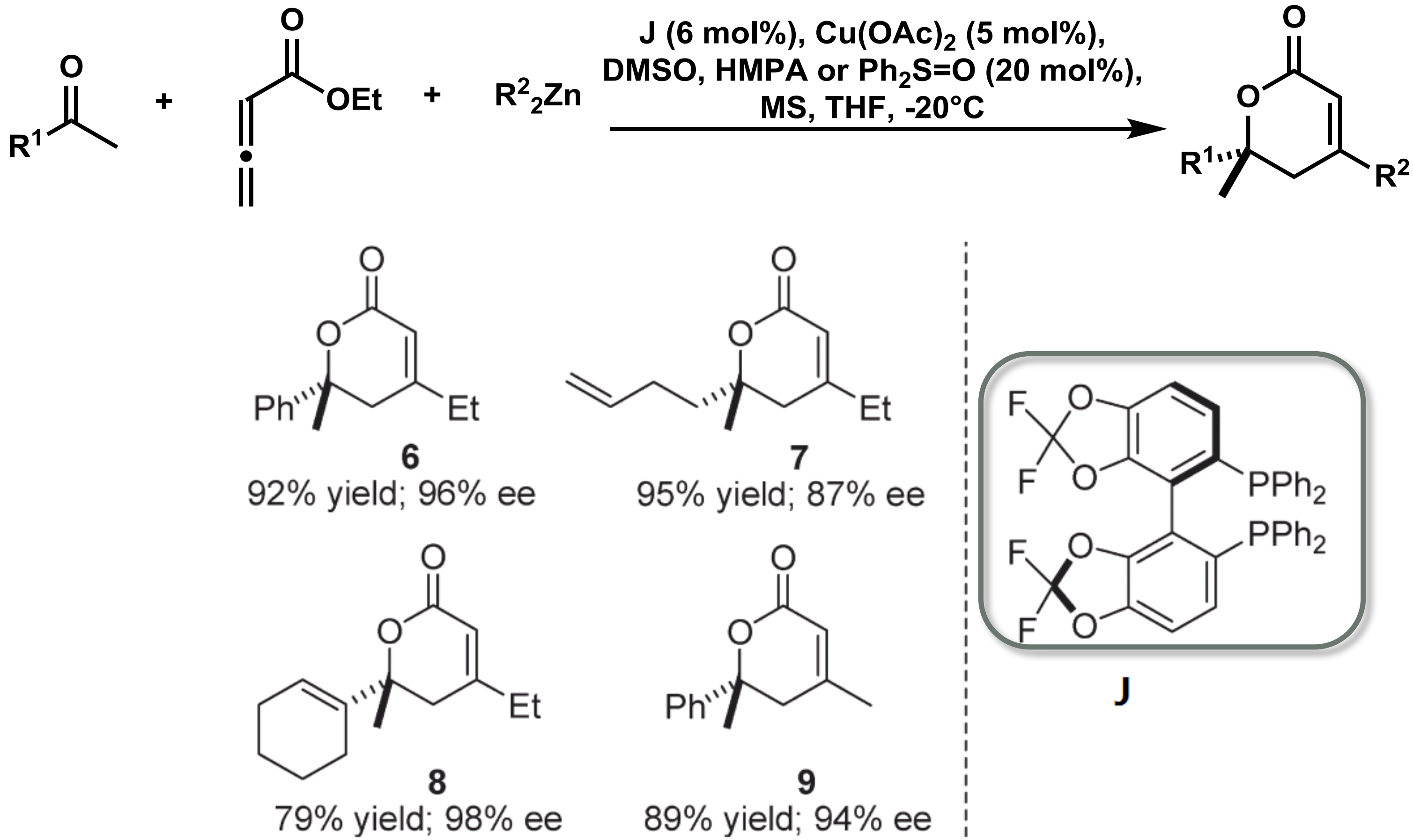


Shibasaki, M. *et al. Tetrahedron Lett.* **2006,** *47,* 1043

Shibasaki, M. et al. *J. Am. Chem. Soc.* **2007,** *129,* 7439

# Enantioselective Processes
## Direct addition of in situ-generated dienolates

- Asymmetric alkylative VAR of Allenic esters to ketones

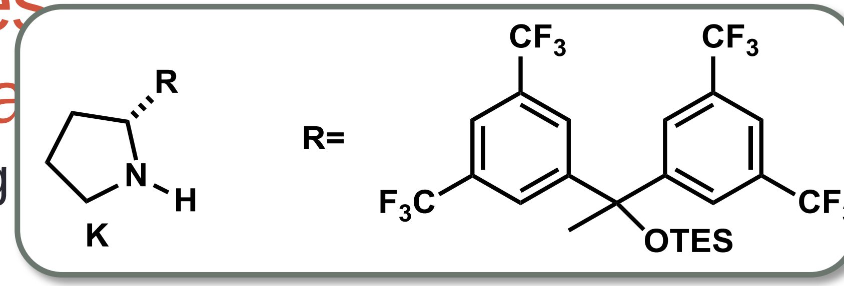


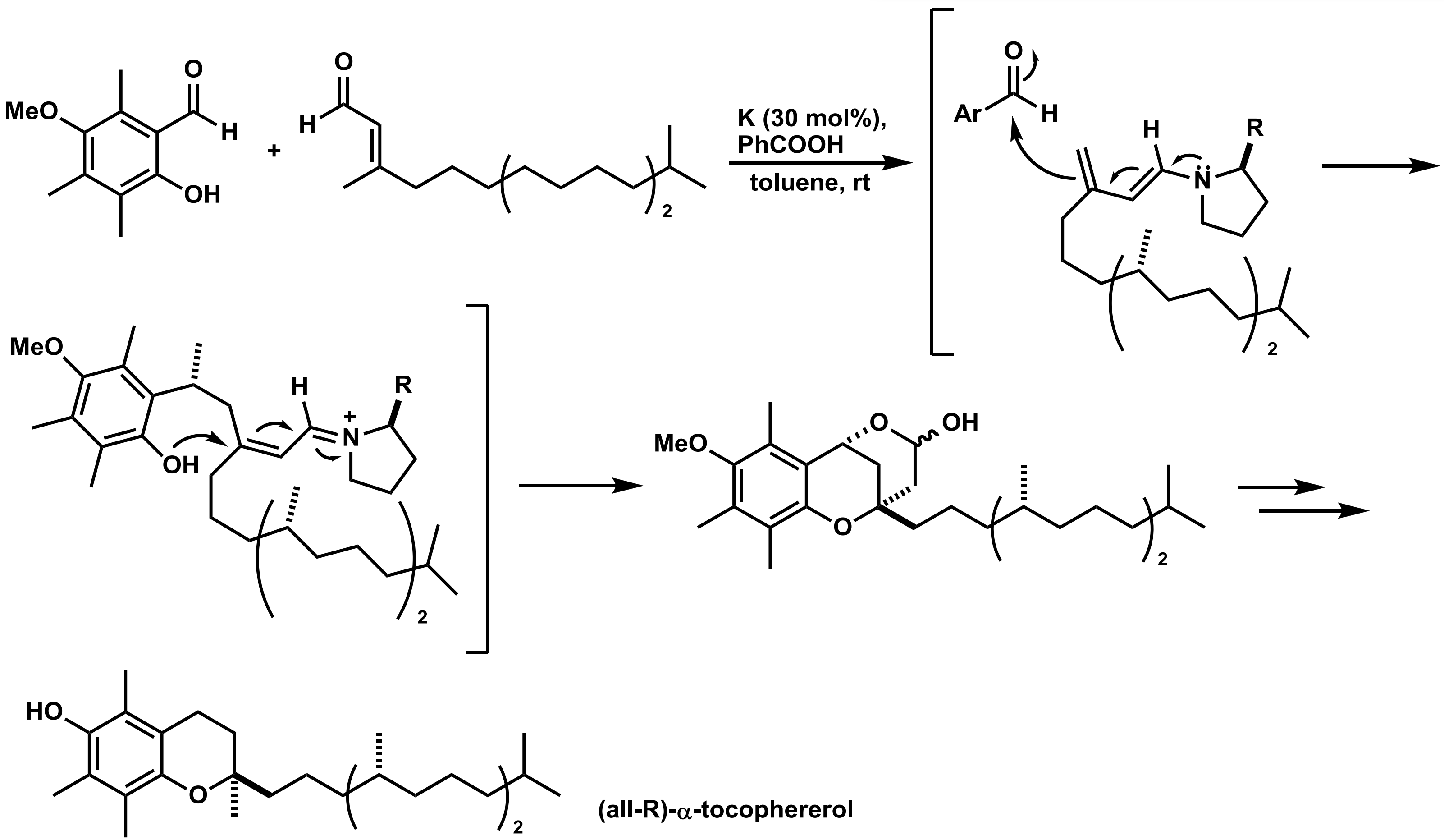

Shibasaki, M. *et al. J. Am. Chem. Soc.* **2007,** *129,* 7439

# Enantioselective Processes

## Direct addition of in situ-genera

- Synthesis of α-Tocopherol highlighting dienamine organocatalysis




(all-R)-α-tocophererol

Liu, K. *et al. Angew. Chem. Int. Ed.* **2008,** *47,* 5827

Thank You for Your Attention!